

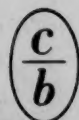
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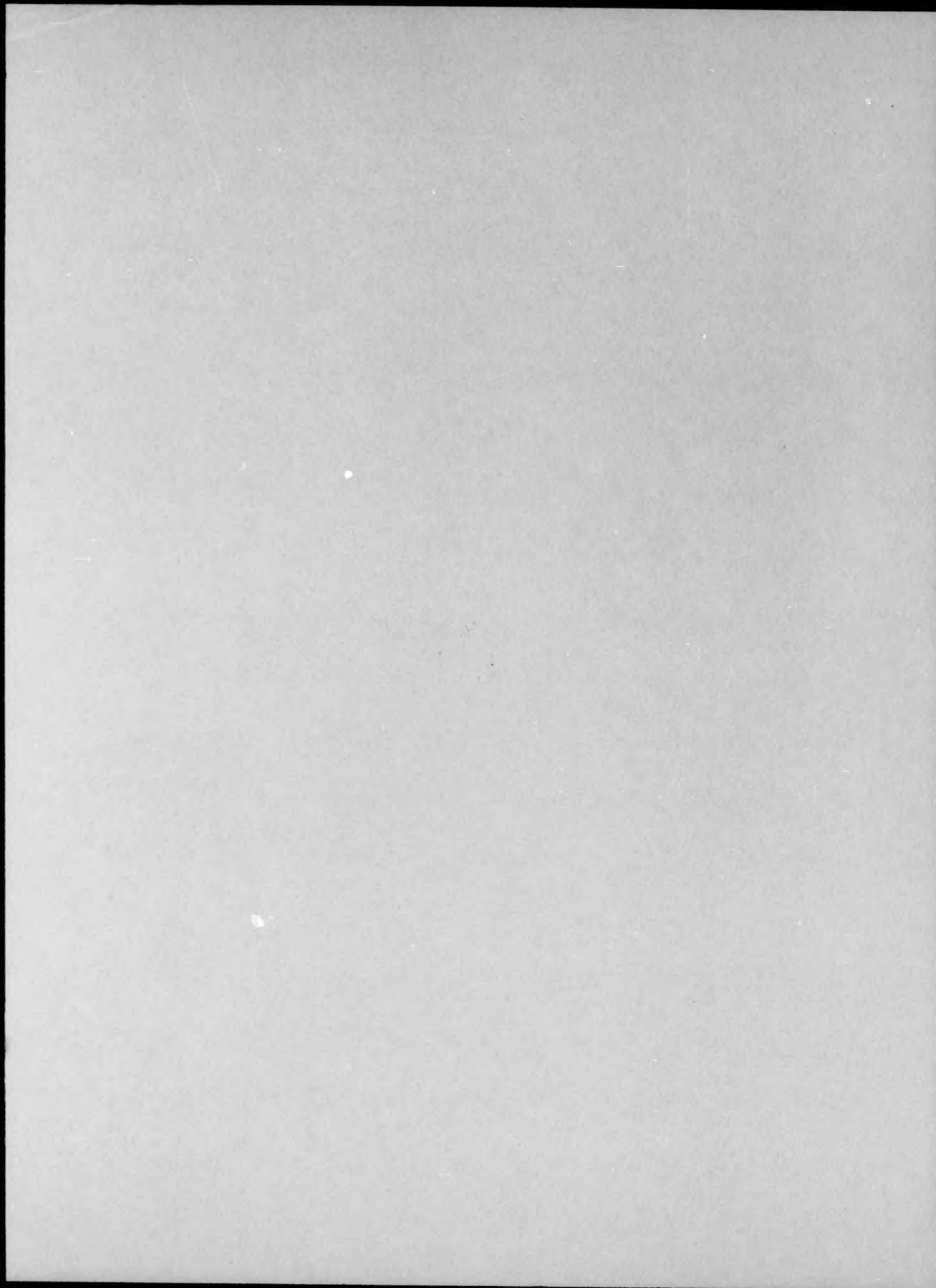
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GIL'M KHAIREVICH KAMAI

# GIL'M KHAIREVICH KAMAI (ON HIS SIXTIETH BIRTHDAY)

A. D. Nikolaeva and V. S. Nikolaev

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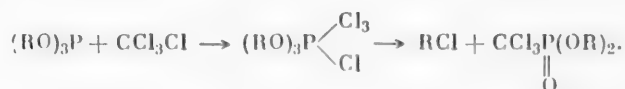
Original article submitted February 1, 1961

G. Kh. Kamai was born on February 23, 1901, to a Tartar longshoreman family in the village of Tetyushi. From early childhood he had to earn his living first as a teamster, a porter, and then as a stevedore. Only the Great October Socialist Revolution made it possible for G. Kh. to obtain an education. He entered the Tartar Teacher's Seminary. In the stern years of the civil war G. Kh. joined the Young Communist League (1918) and was immediately engaged in active propagandistic work.

In May, 1920, G. Kh. was called into the Red Army and was sent to Kazan to attend the courses for officers, and somewhat later he entered the ranks of the Division of the Eastern Political Board of the Revolutionary Military Council of the Republic. In December of 1920 G. Kh. was accepted into the ranks of the Lenin Party. Soon G. Kh. was demobilized and sent to work for the Turkish Bureau of the Central Committee of the Russian Communist Party (Bolsheviks). He stayed about 2 months with the Central Committee, and during this time he had the good fortune to come in close contact with V. I. Lenin, for when attending a session of the Tenth Convention of the Bolshevik party the young communist Kamai had a chance to hear a fiery speech by Lenin. In April of 1921 the Central Committee of the Young Communist League of Russia sent G. Kh. to Omsk as a member of the Siberian-Tartar Bureau at the Siberia Bureau of the Central Committee of the Young Communist League of Russia, where he took an active part in organizing units of the Young Communist League among the Tartar, Kazakh and Khakass youth of Siberia. In 1922 G. Kh. Kamai enrolled in the chemistry section at Tomsk State University.

In the spring of 1926, after brilliantly defending his diploma work on the subject "Concerning the Rate of the Nitration Reaction," G. Kh. remained as a fellow in the department of organic chemistry under the direction of B. V. Tronov, but in December of 1926 he was transferred for the completion of his fellowship to the Kazan State University, where he began to work under the direction of A. E. Arbuzov, occupying himself with a study of organic thiophosphorus compounds [1], the results of which were presented by him at the Fifth Mendeleev Convention. After a successful completion of his fellowship work, the Presidium of the Supreme Council of the National Economy of the USSR sent G. Kh. to Germany to work in the laboratory of the famous chemistry professor Meisenheimer. In Meisenheimer's laboratory G. Kh. made a study of the separation of unsaturated asymmetrical alcohols into the optically active components. He was the first to separate ethylvinylcarbinol into the optical antipodes [2].

On returning to his country, being a student and close co-worker of A. E. Arbuzov, G. Kh. carried out a number of interesting investigations in the field of the synthesis of organophosphorus compounds. He discovered the remarkable reaction of carbon tetrachloride with phosphorous acid esters. Together with L. P. Egorova [3], he found that carbon tetrachloride reacts with the alkyl esters with the liberation of alkyl chloride and the formation of trichloromethylphosphonic acid:



In later studies [4] it was shown that the alkyl esters of arylphosphinic, alkylphosphinic, pyrophosphorous and subphosphoric acids, i.e., all esters containing trivalent phosphorus, tend to react quite easily with carbon tetrachloride. The trichloromethylphosphonic acid esters synthesized by the above indicated reaction have practical interest and can be used as insecticides, fungicides, plasticizers and flame retardants. Together with F. M.



Kharrasova [5], G. Kh. studied the reaction of carbon tetrachloride with the mixed esters of phosphorous acid and established that this reaction leads to the formation of various mixed or unmixed esters of trichloromethylphosphonic acid, with the cleavage of the more volatile phosphite as alkyl chloride. The original interpretation of the mechanism of this reaction was given. Recently G. Kh. Kamai and F. M. Kharrasova worked out a one-step method for the preparation of these esters, consisting in the use of the appropriate alcohols, phosphorus trichloride and carbon tetrachloride as the starting components, and triethylamine as the binding agent for the liberated hydrogen halide. G. Kh. also studied the reaction of phosphorous acid esters with carbon tetrabromide and the haloforms [6].

One of the promising directions in the investigations of G. Kh. [7] is the synthesis of the unsaturated esters of phosphorus-containing acids. The first member of the unsaturated acid esters of phosphorous acid, diallylphosphorous acid, was synthesized by him. Some analogs of triallyl phosphite were prepared. Simultaneously with the American chemist Toy and independently of him, he studied the polymerization of unsaturated organophosphorus compounds.

G. Kh. Kamai and V. A. Kukhtin [8] were the first to synthesize and study a number of unsaturated esters of phosphorous, arylphosphinic, alkylphosphonic, arylphosphonic, alkylarylphosphonic, phosphonocarboxylic and certain  $\alpha$ -ketophosphonic acids. They established that the allyl esters of phenylphosphonic, acetylphosphonic, benzoylphosphonic and allylphosphonic acid, when heated with benzoyl peroxide, can be polymerized with the formation of hard transparent resins similar to the polyacrylates and possessing fire-resistant properties. It was also found that the copolymers of methyl methacrylate with the unsaturated esters of phosphonic acids have a high fire resistance.

Very interesting results were obtained when a detailed study was made of the telomerization of unsaturated acids with trialkyl phosphites. In studying the addition of trialkyl phosphites to  $\alpha, \beta$ -unsaturated acids, G. Kh. in company with V. A. Kukhtin were the first to find that the addition goes with the formation of phosphonocarboxylic acids [9]. This reaction was later extended by the authors to the unsaturated aldehydes and the anhydrides of unsaturated acids. At the present time G. Kh. Kamai, in company with V. S. Tsivunin [10], is engaged in studying the polymerization of a new group of unsaturated organophosphorus compounds.

Enumeration of the investigations of G. Kh. Kamai in the field of organophosphorus compounds would be incomplete if mention was not made of his investigations in the field of asymmetric phosphonium compounds, begun by him many years ago. As a result of these investigations it proved possible to isolate a whole series of asymmetric phosphonium compounds of type  $RR'R''R'''PBr$ , and to show that in salts of phosphonium bases with an optically active anion the cation of the phosphonium base can be optically active [11].

A large number of G. Kh. Kamai's investigations are devoted to the synthesis of organoarsenic compounds and a study of their properties. It is characteristic that G. Kh., still being a young scientist, selected this field of study all by himself. The following fact testifies nicely to the contribution made by G. Kh. to this field of heteroorganic chemistry: of the 350 esters of organoarsenic acids synthesized in the last 100 years, more than half of them were synthesized by G. Kh.

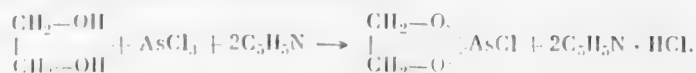
A. E. Arbuzov characterizes the work of Kamai in the field of organoarsenic compounds as follows: "Soviet chemists occupy a relatively modest position in the field of studying arsenic derivatives. The most systematic study of organoarsenic compounds belongs to G. Kh. Kamai. An investigation of asymmetrical arsenic derivatives should be regarded as being the main direction of G. Kh. Kamai's studies" [12].

In company with V. M. Zoroastrova [13], a study of the esters of trivalent arsenic acids was begun by G. Kh. in 1935. In one group of studies in this field G. Kh. set as his goal the preparation of optically active components containing the asymmetric trivalent arsenic atom. In his search for ways of resolving organoarsenic compounds into the optical antipodes G. Kh. accumulated a vast amount of experimental material [14]. One of his original syntheses was the preparation of secondary arylarsenious acids and asymmetrical secondary haloarsines of type  $RR'AsHal$ , and the preparation of asymmetrical analogs of cacodyl oxide, from which he obtained the corresponding arsinic acids of type  $RR'AsR''COOH$ . Preparation of the individual optically active compounds proved to be extremely difficult and it was only because of his great experimental skill that G. Kh. was able to accomplish a whole series of very interesting syntheses. An example of these syntheses is the preparation of the optically active arsonium compounds of type  $RR'R''R'''AsHal$ . For a long time the attempts to separate compounds of this type were unsuccessful, and G. Kh. Kamai was the first to achieve this goal. In 1933 he was able to isolate d-ethylpropyl-p-tolylbenzyl-arsonium iodide by using bromocamphorsulfonate. The doctoral dissertation of G. Kh. Kamai, which he successfully defended in 1941, was devoted to a study of the asymmetrical organic compounds of phosphorus and arsenic.

The last 10-12 years have been devoted by G. Kh. to a very intense and comprehensive study of organoarsenic compounds. A whole series of methods have been proposed by him for the synthesis of these compounds. A very convenient preparative method is the one worked out by G. Kh. for the synthesis of arsenic esters, consisting in the reaction of alcohols with haloarsines in the presence of organic bases, and using absolute ether as the reaction medium.



This method makes it possible to run the reaction under mild conditions and is especially suitable for obtaining the acid chlorides of glycol arsenious acids, for example:



The acid chlorides [15] obtained in this manner proved to be extremely valuable starting materials for the synthesis of various organoarsenic compounds. Various mixed cyclic esters of arsenious acid were synthesized by the reaction of equimolar amounts of these acid chlorides with the appropriate alcohols in the presence of bases and using ether as the reaction medium. G. Kh. was the first to obtain the amides of the cyclic esters of arsenious acid by reacting the acid chlorides with dialkylamines. Since the alkoxyhaloarsines were extremely valuable starting materials, G. Kh. in company with N. A. Chaadaeva [15], worked out still two other original methods for the preparation of these reactive compounds. One of these methods was based on the reaction of the complete cyclic esters of arsenious acid with arsenic trichloride at elevated temperature. The second method is very simple experimentally. It consists in reacting the complete esters of arsenious acid with acetyl chloride. The last method was extended successfully to the esters of ethylarsinic and phenylarsinic acids.

A large amount of work was devoted by G. Kh. to a study of the properties of the synthesized compounds. Such chemical properties of the esters of trivalent arsenic as the transesterification reaction of the esters with alcohols and trialkoxystibines, the decomposition of the amidoesters and thioesters with alkyl halides, the tendency of the allyl esters to polymerize and copolymerize, the behavior of various esters of the alkyl and dialkylarsinic acids when heated, and also of the trialkylarsine oxides, first became known as a result of the studies of G. Kh. and his co-workers. A whole series of investigations was devoted by G. Kh. to a study of the structure of the synthesized compounds. Together with L. M. Starshov [16], he determined the atomic refraction of arsenic in various groups of esters of arsenious acid. Using the parachor method, G. Kh. Kamai and K. I. Kuz'min [17] studied the fine structure of the molecules of the esters of arsenious acid, arsenic acid and trialkylarsines. Much of G. Kh. Kamai's work was devoted to a comparative study of the properties of the esters of trivalent phosphorus acids and the esters of trivalent arsenic acids. It was shown that the esters of arsenious acid, in contrast to the analogous esters of phosphorous acid, do not isomerize with the formation of esters of pentavalent arsenic, i.e., rearrangement does not take place in the given case, known as the Arbuzov rearrangement for the case of the esters of phosphorous acid. However, G. Kh. was able to distinctly show that many esters of trivalent arsenic acids react in a manner analogous to the first step of the Arbuzov rearrangement: they possess the ability to add electrophilic reagents with the formation of crystalline products. It was found that the esters of the alkylarsinic and dialkylarsinic acids form crystalline compounds of the arsonium type when reacted with alkyl halides. Similar to the esters of phosphorous acid, the esters of diphenylarsinic, alkylphenylarsinic and alkylarsinic acids react with cuprous halides.

Specialists are also familiar with the studies of G. Kh. in other fields of organic chemistry. The results of the investigations carried out by Kamai are reflected in the publication of 220 papers, and he also has 31 patents to his credit. The far from complete survey given above of the research work of Kamai is but one facet of his many-sided activity.

G. Kh. Kamai devoted more than 30 years to teaching, coupling it with responsible administrative work. In 1931 G. Kh. Kamai became professor at the V. I. Ul'yanov-Lenin Kazan State University and the S. M. Kirov Kazan Chemical-Technological Institute. In the latter, with the active participation of G. Kh., a department of intermediate products and dyes was organized, which he subsequently directed. From 1935 to 1937 G. Kh. was rector of the Kazan State University, and during 1930-1931 and 1944-1945 he was substitute director of research at the Kazan Chemical-Technological Institute. Much energy and time was contributed by G. Kh. to organizing the Kazan branch of the Academy of Sciences of the USSR. From the time the branch was organized until 1952 he was scientific secretary of the section. In 1946 G. Kh. created the Department of the Technology of Organic Synthesis, having a broad scope, in the Kazan Chemical-Technological Institute.

The work on 16 candidates' and 2 doctoral dissertations was carried out under the supervision of Prof. G. Kh. Kamai. More than a 1000 chemical engineers were trained in the department headed by G. Kh. Kamai. For his service to the Country, both in the field of scientific investigations and in the training of young chemists, G. Kh. Kamai had bestowed on him two Orders of the Workers Red Cross, the Order of the Badge of Honor, a medal "For valorous duty in the Great Patriotic War, 1941-1945," and the honor "Distinguished Member of the Socialistic Competition of MOM of the USSR."

For his investigations in the field of organic phosphorus and arsenic compounds G. Kh. Kamai was awarded the Stalin prize by order of the Council of Ministers of the USSR on March 12, 1952.

Much time and effort is donated by G. Kh. Kamai to the dissemination of scientific knowledge. He frequently delivers papers before highly different audiences. G. Kh. Kamai has been a member of the Mendeleev Society since 1926 and a member of the Society for the Propagation of Political and Scientific Knowledge since 1947.

G. Kh. is well known in the scientific world as a talented research chemist, as an able organizer, and as an energetic social worker.

Simplicity and sincerity are a characteristic feature of G. Kh. Kamai's attitude toward people. The people know and prize these traits, repeatedly electing him to the Kazan City Council of Deputies of the Working Class. In 1959 G. Kh. was elected a delegate to the 21st Convention of the Communist Party of the Soviet Union.

The entire life of Professor G. Kh. Kamai is an example of unselfish labor for the good of the Soviet people, in the name of peace on earth and a more rapid building up of Communism.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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# DETERMINATION OF THE SATURATED VAPOR PRESSURE OF INDIUM OXIDE

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It is known [1] that the long heating of  $\text{In}_2\text{O}_3$  at temperatures up to  $1200^\circ$  fails to cause any change in the weight of the oxide. An attempt [2] to measure the saturated vapor pressure of indium oxide at  $1060^\circ$  by the flow method proved unsuccessful: no change was observed in the weight of the oxide. These few published data suggest that indium oxide has a very low vapor pressure. On the other hand, it was indicated [3] that  $\text{In}_2\text{O}_3$  undergoes some thermal decomposition in vacuo. Starting with these facts, we rejected the methods of determining the vapor pressure based on heating the substance in a high vacuum, and instead adopted higher temperatures ( $1290-1490^\circ$ ) and the flow method for our experiments, using air as the gas-carrier, which tends to suppress the dissociation of  $\text{In}_2\text{O}_3$ . The use of pure oxygen is not obligatory in the given case, since indium nitride burns in air when ignited [1]. In the case of using the flow method the saturated vapor pressure is calculated using the equation:

$$p_1 = \frac{np_2}{N + n}, \quad (1)$$

where  $p_1$  is the saturated vapor pressure of the investigated substance,  $p_2$  is the pressure of the gas-carrier,  $N$  is the number of moles of the gas-carrier, and  $n$  is the number of moles of the vaporized substance.

The method of radioactive indicators was used to increase the sensitivity. As the radioactive isotope we used  $\text{In}^{114}$ , with a half-life period of 48.5 days. Knowing the specific activity of the material and the change in activity due to vaporization of the substance, it becomes possible to calculate the amount of  $\text{In}_2\text{O}_3$  vaporizing per unit of time. Equation (1) assumes the following form:

$$p_1 = \frac{\frac{q\Delta C}{CM} p_2 \cdot 22.4}{V_0 + \frac{q\Delta C}{CM}}, \quad (2)$$

where  $q/C$  is the specific activity of the material,  $\Delta C$  is the change in activity due to loss of substance,  $V_0$  is the volume, reduced to standard conditions, of air passed over the substance (in liters), and  $M$  is the molecular weight of  $\text{In}_2\text{O}_3$ . In the calculations we assumed that the  $\text{In}_2\text{O}_3$  exists as the monomer in the vapors.

## EXPERIMENTAL

Metallic indium containing radioactive  $\text{In}^{114}$  was dissolved in dilute hydrochloric acid. After precipitation with ammonia, the indium hydroxide was washed with water until the wash waters gave a negative test for chloride ion; then it was dried at  $150-160^\circ$  and ignited at  $1000^\circ$  for 4-5 hr. After this the material was ignited at  $1200^\circ$  for 1 hour. The radiochemical purity of the material was checked using a  $\gamma$ -spectrometer. It was found that the amount of undeciphered  $\gamma$ -lines did not exceed 3% of the total activity of the material.

A diagram of the apparatus built by us for making the study is shown in Fig. 1. The indium oxide was placed in alundum boat 2 fastened to the end of quartz tube-holder 14. In turn, the holder was inserted in a quartz tube heated in a Type VT-40/400 tube furnace 1. The temperature in the alundum boat was measured with a Pt-PtRh thermocouple 3, using a PP-1 potentiometer. The apparatus was built in such manner that the alundum boat could be removed from the hot zone of the furnace without upsetting the airtightness of the apparatus. A block counter 10, enclosed by a protective lead cover 11, was used to determine the change in the activity of the material. The air entering the furnace was first dried with sulfuric acid 4,  $\text{CaCl}_2$  5 and 8,  $\text{P}_2\text{O}_5$  6, and liquid oxygen 7. The rate

of gas flow was measured with a GSB-400 gas meter 9. An alundum diaphragm 15, serving to reduce the back diffusion of  $\text{In}_2\text{O}_3$  vapors, was installed in the hot zone of the furnace. The ground-glass connections 13 were cooled with water. Before placing under the window of the counter, the boat with material, after removal from the furnace, was first cooled in the zone surrounded by water jacket 12.

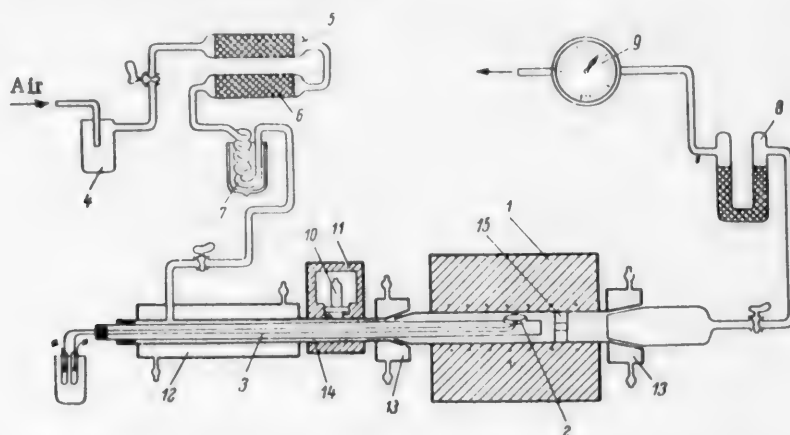


Fig. 1. Diagram of apparatus for measuring low vapor pressures by the flow method, using radioactive isotopes. Explanation in text.

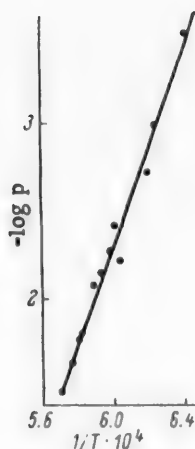


Fig. 2. Saturated vapor pressure of  $\text{In}_2\text{O}_3$  as a function of temperature.

In the preliminary experiments we measured the flow rate of the gas-carrier corresponding to the state of its saturation with  $\text{In}_2\text{O}_3$  vapors. This rate was determined for three temperatures: 1290, 1445 and 1490°. In extrapolating to zero rate, we did not take into account the value of the molar concentration of  $\text{In}_2\text{O}_3$  at flow rates less than 4 ml/min, where a considerable scattering of the points was observed. We selected a flow rate of 5–7 ml/min. The values of the molar concentration of  $\text{In}_2\text{O}_3$ , obtained by extrapolation to zero rate and those measured at gas-carrier flow rates of 5–7 ml/min did not differ by more than 8%.

The saturated vapor pressure of  $\text{In}_2\text{O}_3$  was measured in the interval 1290–1490°. The results of the measurements are plotted in Fig. 2 (for three independent experiments with materials of different specific activity).

The dependence of the saturated vapor pressure of indium oxide on the temperature can be described by the following equation:

$$\log p = -\frac{27791}{T} + 14.353. \quad (3)$$

The main error in determining the absolute values of the vapor pressure of indium oxide is composed of the following terms: the error in determining the specific activity of the material ( $\pm 1.2\%$ ), the error in measuring the activity ( $\pm 6.0\%$ ), the error in determining the temperature of the sample ( $\pm 0.5\%$ ), and the error in measuring the volume of the gas passed through ( $\pm 2.0\%$ ). The error in measuring the pressure, calculated on the basis of these values for Equation (2), is  $\pm 6.0\%$ .

The enthalpy value of  $\text{In}_2\text{O}_3$  sublimation for the temperature range 1290–1490° was found to be equal to  $118 \pm 2$  kcal/mole. Since information on the heat capacity of indium oxide at elevated temperatures is lacking in the literature, we estimated the entropy value of the  $\text{In}_2\text{O}_3$  sublimation process, using in the calculation the value of  $C_p$  for the temperature range from 0 to 100° [1]. We obtained for  $\Delta S^\circ$  the value  $42 \pm 1$  kcal/mole·°C.

#### SUMMARY

1. An apparatus was built for measuring low vapor pressures by the flow method, using radioactive isotopes.
2. The saturated vapor pressure of  $\text{In}_2\text{O}_3$  was measured in the temperature range 1290–1490°.
3. On the basis of the obtained experimental data the heat and the entropy of  $\text{In}_2\text{O}_3$  sublimation were found to be equal to  $118 \pm 2$  kcal/mole and  $42 \pm 1$  kcal/mole·°C, respectively.

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# STUDY OF THE STRUCTURE OF $\delta$ -KETO ACIDS BY THE INFRARED SPECTROSCOPY METHOD

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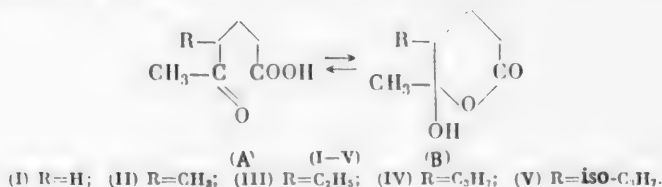
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It is known that some  $\alpha, \beta$ -unsaturated and aromatic  $\gamma$ -keto acids exist in the form of hydroxylactones. A hydroxylactone (lactol) structure was proved by the ultraviolet spectroscopy method for several  $\beta$ -aroylacrylic acids [1] and by the infrared spectroscopy method for penicillic acid [2], acetophenone-*o*-carboxylic acid, and for other acids of this type [3,4]. The infrared spectra of the studied acids were found to contain absorption bands corresponding to the C=O and OH valence vibrations of the cyclic hydroxylactone forms, while the absorption bands of the open keto forms were absent.

The purpose of the present work was to elucidate the structure of the  $\delta$ -keto acids (I-V), for which some authors [5] postulated the possibility of ring-chain tautomeric transformations.



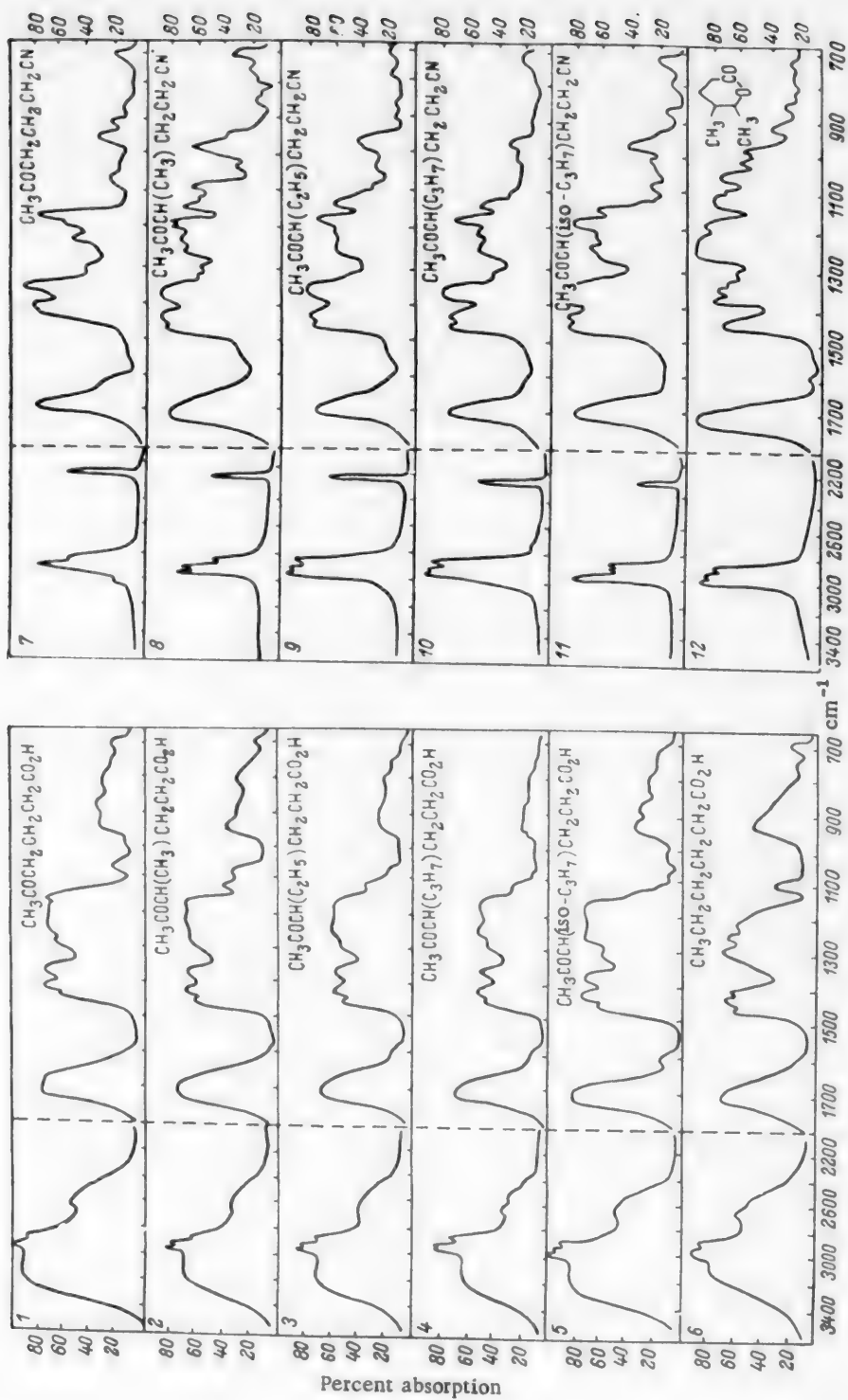
To answer the question of the structure of the  $\delta$ -keto acids (I-V) we studied their infrared spectra, and also the infrared spectra of the  $\delta$ -keto nitriles (VII-XI), as being compounds with a carbon skeleton close to the skeleton of the open form of the  $\delta$ -keto acids (A), and the spectrum of the saturated  $\delta$ -lactone (XII) (5,6-dimethyltetrahydro- $\alpha$ -pyrone), as being a model compound with a structure close to the structure of the postulated lactols (B).

The  $\delta$ -keto nitriles and  $\delta$ -keto acids were synthesized by previously developed methods [6-8].  $\delta$ -Lactone (XII) was obtained (40% yield) by the reduction of  $\delta$ -keto acid (II) with sodium in alcohol [9] or with sodium amalgam [10]. The constants of all of the compounds agreed with the literature data [6,7,9,11].

We used both an IRS-2 and an IRS-11 machine to record the infrared spectra of these compounds, employing a LiF prism for the 3600-2000 cm<sup>-1</sup> region and a NaCl prism for the 1800-700 cm<sup>-1</sup> range. The layer thickness in the KBr cell ranged from 0.005 to 0.03 mm. The spectra of the synthesized compounds, as well as the comparison spectrum of *n*-caproic acid (VI), are shown in the chart (Nos. 1-12). A comparison of the spectra reveals that the absorption curve of the  $\delta$ -keto acids (I-V) in the 3600-2000 cm<sup>-1</sup> region has the appearance characteristic for associated aliphatic acids, with a maximum in the range 2665-2642 cm<sup>-1</sup> and a broad absorption band in the range 3200-3000 cm<sup>-1</sup> (OH valence vibrations of the carboxyl). An intense absorption band with a maximum around 3200 cm<sup>-1</sup> [2-4], which is absent in the spectra of acids (I-V), is characteristic for the OH valence vibrations of the earlier mentioned lactols.

As a result, an examination of the spectra in the 3600-2000 cm<sup>-1</sup> region makes it possible to conclude that the  $\delta$ -keto acids have the open keto structure (A). This conclusion is also supported by an examination of the spectra in the 1800-700 cm<sup>-1</sup> region. As is known, the characteristic vibrations of the associates of aliphatic acids associated with the carboxyl group give in the liquid state broad absorption bands at 935  $\pm$  15 cm<sup>-1</sup>, 1300  $\pm$  15 cm<sup>-1</sup>, ~1400 cm<sup>-1</sup>, and at 1725  $\pm$  4 cm<sup>-1</sup> [12].

All of the studied  $\delta$ -keto acids (I-V) absorb in the regions 1300  $\pm$  15 cm<sup>-1</sup> and 935  $\pm$  15 cm<sup>-1</sup>, in which connection the first of these bands (absorption at 1297  $\pm$  3 cm<sup>-1</sup>) is especially distinct in the spectra of acids (I-V);





the second band is weak in intensity and is masked by the absorption at  $962-965\text{ cm}^{-1}$  observed also for the  $\delta$ -keto nitriles (VII-XI). In the  $1400\text{ cm}^{-1}$  region an absorption band at  $1415 \pm 3\text{ cm}^{-1}$  was observed for all of the studied  $\delta$ -keto acids (I-V), and a band at  $1425 \pm 3\text{ cm}^{-1}$  was observed for all of the  $\delta$ -keto nitriles (VII-XI).

In the case of the  $\delta$ -keto nitriles this absorption band is associated only with the deformation C-H vibrations of the methyl and methylene groups, the frequency of which changes under the influence of adjacent C=O and CN groups. A similar reduction in the frequency of C-H vibrations under the influence of an adjacent C=O group was observed for acetone (absorption at  $1431\text{ cm}^{-1}$ ) [13], for methyl alkyl ketones (absorption at  $1420\text{ cm}^{-1}$ ) [13], and for carboxylic acid esters (absorption at  $1410\text{ cm}^{-1}$ ) [14]. For acids containing the grouping  $\text{CH}_2\text{CO}_2\text{H}$  it was shown that the characteristic absorption around  $1400\text{ cm}^{-1}$  is associated with the deformation C-H vibrations, as well as with the carboxyl group itself [15].

In the case of the  $\delta$ -keto acids (I-V), the absorption band at  $1415 \pm 3\text{ cm}^{-1}$  is also associated with the C-H vibrations of the methyl and methylene groups adjacent to the keto and carboxyl C=O groups, as well as with the COOH group. This is supported by the greater intensity of this band than in the case of the nitriles when  $\delta$ -keto nitriles and  $\delta$ -keto acids with the same number of C-H linkages in the  $\alpha$ -position to the C=O and CN or C=O and  $\text{CO}_2\text{H}$  groups are compared.

As regards the absorption in the  $1700\text{ cm}^{-1}$  region (C=O valence vibrations), in our case the data for this region cannot serve as a criterion for establishing the structure of the  $\delta$ -keto acids. In contrast to the earlier studied  $\gamma$ -keto acids [2, 4], where the frequencies of the C=O valence vibrations of the keto and hydroxylactone forms differ strongly, in the case of the  $\delta$ -keto acids the frequency of the C=O valence vibrations of the keto form and that of the postulated lactone form have close values ( $1720 \pm 1\text{ cm}^{-1}$  for methyl alkyl ketones,  $1725 \pm 4\text{ cm}^{-1}$  for acids, and  $1740-1738\text{ cm}^{-1}$  for  $\delta$ -lactones). A broad band at  $1729-1726\text{ cm}^{-1}$  was found to be present for the studied  $\delta$ -keto acids. The nitriles absorbed at  $1717\text{ cm}^{-1}$ .

An examination of the  $1140-980\text{ cm}^{-1}$  region (vibrations of the skeleton) reveals that the nitriles and acids with identical radicals show approximately the same absorption in this region, giving either one or two absorption bands at  $1095-1067$  and at  $1144-1127\text{ cm}^{-1}$  of variable intensity. The second band in this region (absorption at  $1144-1127\text{ cm}^{-1}$ ) is absent for  $\gamma$ -acetylbutyric acid (I) and for the nitrile of this acid, and is observed for all of the other acids and nitriles, which enables assigning it to the C-CH<sub>3</sub> vibrations.

The approximately identical absorption shown by  $\delta$ -keto nitriles and  $\delta$ -keto acids in the region of the skeletal vibrations can serve as additional conclusive proof that the  $\delta$ -keto acids (I-V) have the open keto structure (A). On the other hand, the  $\delta$ -lactone (XII) (5, 6-dimethyltetrahydro- $\alpha$ -pyrone) differs from the  $\delta$ -keto acids and  $\delta$ -keto nitriles by an intense absorption in the  $1140-970\text{ cm}^{-1}$  region (bands at  $975, 1008, 1047$  and  $1100\text{ cm}^{-1}$ ) which is associated with its cyclic structure. It is known that such oxygen-containing heterocycles as  $\delta$ -valerolactone (band at  $1056\text{ cm}^{-1}$ ) [16], tetrahydropyran (bands at  $1097$  and  $1050\text{ cm}^{-1}$ ) [17] and 2, 6-dimethyl-3-acetoxytetrahydropyran (bands at  $1080, 1030$  and  $1000\text{ cm}^{-1}$ ) [18] show strong absorption in the  $1100-1080\text{ cm}^{-1}$  region.

#### SUMMARY

The infrared spectra of the  $\delta$ -keto acids all exhibit absorption bands characteristic of the carboxyl group, while the absorption bands of the cyclic lactol forms are absent, which proves the open (completely or predominantly) keto structure (A) of the  $\delta$ -keto acids. The fact that the  $\delta$ -keto acids and the  $\delta$ -keto nitriles have approximately the same absorption in the region of the skeletal vibrations supports this conclusion.

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# VINYL COMPOUNDS IN DIENE SYNTHESIS

## VII. DIENE SYNTHESIS OF VINYL ETHERS AND THIOETHERS

### WITH 2, 3-DIMETHYL-1, 3-BUTADIENE

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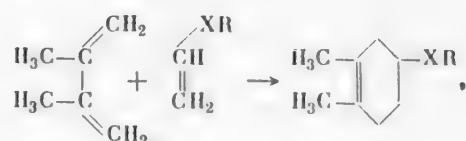
Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 7,

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Original article submitted July 11, 1960

Earlier it was reported [1-3] that the vinyl and thiovinyl ethers are capable of entering into diene synthesis with certain cyclic dienes. Based on this reaction, a series of new adducts which are aldrin and dihydroaldrin derivatives were synthesized by the reaction of vinyl ethers and thioethers with cyclopentadiene and hexachlorocyclopentadiene. In this connection it was observed that the vinyl aryl and thiovinyl ethers enter into this reaction more easily than do the vinyl alkyl ethers, and that the diene synthesis of cyclopentadiene and hexachlorocyclopentadiene with thiovinyl ethers goes the easiest and at lower temperatures.

For the purpose of making a further systematic study of the diene synthesis reaction involving vinyl ethers, and also for elucidating their comparative dienophilic activity when reacted with dienes of variable structure, we investigated the reaction of vinyl and thiovinyl ethers with 2, 3-dimethyl-1, 3-butadiene, which is one of the active noncyclic dienes [4-7]. The vinyl ethers used in the diene synthesis were vinyl phenyl, vinyl cyclohexyl, vinyl n-hexyl and vinyl n-decyl ethers, and also vinyl ethyl and vinyl phenyl sulfides. The reaction goes in accordance with the scheme:



where XR = OC<sub>6</sub>H<sub>5</sub> (I), OC<sub>6</sub>H<sub>11</sub> (cyclo) (II), OC<sub>6</sub>H<sub>13</sub> (III), SC<sub>6</sub>H<sub>5</sub> (IV), SC<sub>2</sub>H<sub>5</sub> (V). This reaction is accompanied by the copolymerization of the starting vinyl compounds with the 2, 3-dimethyl-1, 3-butadiene, which, as is known [8], polymerizes easily when heated.

The diene synthesis reaction was run in a steel ampul, using temperatures ranging from 170 to 230° and a variable reaction time. Observation revealed that the vinyl phenyl and vinyl cyclohexyl ethers react most easily in the diene synthesis reaction with 2, 3-dimethyl-1, 3-butadiene, while the vinyl n-hexyl ether reacts with the greatest difficulty. In the case of vinyl n-decyl ether the adduct could not be isolated under the investigated conditions and most of the starting ether was recovered unchanged. The diene synthesis of 2, 3-dimethyl-1, 3-butadiene with the vinyl ethyl and vinyl phenyl sulfides went at lower temperatures, but the adducts were obtained in lower yields than in the case of cyclopentadiene, which is probably due to the instability of the adducts under the synthesis conditions.

## EXPERIMENTAL

1. Reaction of vinyl phenyl ether with 2, 3-dimethyl-1, 3-butadiene. • A mixture of 24 g (0.2 mole) of vinyl phenyl ether and 8.2 g (0.1 mole) of 2, 3-dimethyl-1, 3-butadiene was heated in a steel ampul at 230-235°

• Obtained from the pinacol hydrate [9].

for 12 hr in the presence of 0.1% hydroquinone. The excess vinyl phenyl ether and the 2, 3-dimethyl-1, 3-butadiene dimer were removed by distillation, and the residue was fractionally distilled to give the following fractions: 1st, b.p. 145–160° (10 mm), 9.5 g; 2nd, b.p. 160–210° (10 mm), 1.5 g; residue 9.5 g. The 1st fraction, after removal of the diphenyl acetal by refluxing with 5% H<sub>2</sub>SO<sub>4</sub> solution [1], extraction and drying, was 1-phenoxy-3,4-dimethyl-3-cyclohexene (I) (see table). The yield of product, based on the 2, 3-dimethyl-1, 3-butadiene, was 47%. The tarry residue was dissolved in ether and treatment of the solution with methanol led to the precipitation of a very viscous, light yellow polymeric product, which after drying at 60° (5 mm) had the following composition (in %): C 84.12, 84.18; H 8.75, 8.78, which corresponds to the copolymer of 2,3-dimethyl-1, 3-butadiene with vinyl phenyl ether, containing 37.1 mole % of vinyl phenyl ether.

2. Reaction of vinyl cyclohexyl ether with 2, 3-dimethyl-1, 3-butadiene. A mixture of 25.2 g (0.2 mole) of vinyl cyclohexyl ether and 8.2 g (0.1 mole) of 2, 3-dimethyl-1, 3-butadiene was heated at 230° for 11 hr. After removal of the excess vinyl cyclohexyl ether and the 2, 3-dimethyl-1, 3-butadiene dimer the following fractions were collected: 1st, b. p. 110–150° (10 mm), 9 g; 2nd, b.p. 150–200° (10 mm), 0.5 g; residue 12 g. The 1st fraction was worked up in the usual manner to give 1-cyclohexoxy-3,4-dimethyl-3-cyclohexene (II) (see table). Yield 43.3%. From the tarry residue by reprecipitation with methanol from ether solution we isolated a very viscous polymeric product of composition (in %): C 82.61, 82.41; H 11.47, 11.43, which corresponds to the copolymer of 2, 3-dimethyl-1, 3-butadiene with vinyl cyclohexyl ether, containing 35.4 mole % of vinylcyclohexyl ether.
3. Reaction of vinyl n-hexyl ether with 2, 3-dimethyl-1, 3-butadiene. A mixture of 25.6 g (0.2 mole) of vinyl n-hexylether and 8.2 g (0.1 mole) of 2, 3-dimethyl-1, 3-butadiene was heated at 220° for 10 hr. After removal of excess ether and the 2, 3-dimethyl-1, 3-butadiene dimer, the following fractions were collected: 1st, b.p. 100–135° (7 mm), 7 g; 2nd, b. p. 135–185° (7 mm), 1.3 g; residue 8 g. From the 1st fraction, after the usual workup, we isolated 1-n-hexoxy-3, 4-dimethyl-3-cyclohexene (III) (see table). Yield 33.3%. From the tarry residue by reprecipitation with methanol from ether solution we isolated a very viscous polymeric product of composition (in %): C 82.30, 82.36; H 11.80, 11.83, which corresponds to the copolymer of 2, 3-dimethyl-1,3-butadiene with vinyl n-hexyl ether, containing 32.5 mole % of vinyl n-hexyl ether.
4. Reaction of vinyl n-decyl ether with 2, 3-dimethyl-1, 3-butadiene. A mixture of 36.8 g (0.2 mole) of vinyl n-decyl ether and 8.2 g (0.1 mole) of 2, 3-dimethyl-1, 3-butadiene was heated at 230° for 13 hr. When the mixture was fractionally distilled we recovered 32.9 g (89.4%) of the starting vinyl n-decyl ether and a small amount of polymeric product.
5. Hydrogenation of obtained adducts. A solution of 3 g of 1-phenoxy-3, 4-dimethyl-3-cyclohexene in 25 ml of methanol was saturated with hydrogen in the presence of Raney-Ni at 40–50° for 3–4 hr. After removal of the solvent the product was distilled to give 2.94 g (98%) of 1-phenoxy-3, 4-dimethylcyclohexane (VI) (see table). The analogous hydrogenation of 1-cyclohexoxy-3, 4-dimethyl-3-cyclohexene and 1-n-hexoxy-3, 4-dimethyl-3-cyclohexene gave, respectively, 1-cyclohexoxy-3, 4-dimethylcyclohexane (VII) and 1-n-hexoxy-3, 4-dimethylcyclohexane (VIII), which were obtained in good yields (see table).
6. Reaction of vinyl phenyl sulfide with 2, 3-dimethyl-1, 3-butadiene. A mixture of 27.2 g (0.2 mole) of vinyl phenyl sulfide and 8.2 g (0.1 mole) of 2, 3-dimethyl-1, 3-butadiene was heated at 180–185° for 15 hr. The excess vinyl phenyl sulfide was removed by distillation, followed by fractional distillation of the product. Here the following fractions were collected: 1st, b. p. 95–145° (5 mm), 6 g; 2nd, b. p. 145–190° (5 mm), 0.5 g; residue 7.5 g. From the 1st fraction we isolated 1-thiophenyl-3, 4-dimethyl-3-cyclohexene (IV). Yield 27.4%. From the tarry residue by reprecipitation with methanol from ether solution we isolated a viscous polymeric product, which after drying at 60° (10 mm) had the composition (in %): C 76.26, 76.29; H 8.85, 8.68; S 15.12, 15.17, which corresponds to the copolymer of 2, 3-dimethyl-1, 3-butadiene with vinyl phenyl sulfide, containing 50.4 mole % of vinyl phenyl sulfide.
7. Reaction of vinyl ethyl sulfide with 2, 3-dimethyl-1,3-butadiene. A mixture of 12.6 g (0.2 mole) of vinyl ethyl sulfide and 8.2 g (0.1 mole) of 2, 3-dimethyl-1, 3-butadiene was heated at 175° for 12 hr. After removal of the vinyl ethyl sulfide by distillation we collected the following fractions: 1st, b. p. 80–110° (5 mm), 6.5 g; 2nd, b. p. 110–140° (5 mm), 0.3 g; residue 7 g. Redistillation of the 1st fraction gave 1-thioethyl-2, 3-dimethyl-3-cyclohexene (V). Yield 38.2%. From the tarry residue by reprecipitation with methanol from ether solution we isolated a viscous polymeric product of composition (in %): C 69.84, 69.62; H 10.49, 10.46; S 19.67, 19.67, which corresponds to the copolymer of 2, 3-dimethyl-1, 3-butadiene with vinyl ethyl sulfide, containing 53.3 mole % of vinyl ethyl sulfide.

Compound No.	Compound	Boiling point (pressure in mm)	$n_D^{20}$	$d_4^{20}$	$M_R$		Found (%)			Empirical formula	Calculated (%)		
					found	calc.	C	H	S		C	H	S
(I)		130—131° (6)*	1.5400	1.0212	62.16	62.23	83.22, 83.00	9.00, 8.81	—	$C_{14}H_{18}O$	83.12	8.96	—
(II)		119.5 (7)**	1.4852	0.9419	63.40	63.53	80.53, 80.77	11.41, 11.41	—	$C_{14}H_{24}O$	80.71	11.61	—
(III)		110 (5)***	1.4572	0.8862	64.63	65.83	79.56, 79.63	12.12, 12.20	—	$C_{14}H_{26}O$	79.93	12.45	—
(IV)		108 (4)	1.5540	0.9999	69.66	68.55	76.68, 76.72	8.48, 8.52	15.05, 15.00	$C_{14}H_{18}S$	77.01	8.31	14.68
(V)		81 (4)	1.5069	0.9424	53.75	53.68	70.68, 70.70	10.51, 10.47	18.73, 18.92	$C_{10}H_{18}S$	70.52	10.65	18.82
(VI)		142—142.5 (10)	1.5298	1.0060	62.71	62.63	82.32, 82.50	9.63, 9.54	—	$C_{14}H_{20}O$	82.30	9.86	—
(VII)		121 (7)	1.4760	0.9286	63.87	63.99	79.64, 79.45	12.50, 12.56	—	$C_{14}H_{26}O$	79.93	12.45	—
(VIII)		112.5—113 (5.5)	1.4450	0.8645	65.37	66.29	78.86, 78.92	13.15, 13.17	—	$C_{14}H_{28}O$	79.17	13.28	—

\* F. p. 58°.

\*\* F. p. 70°.

\*\*\* Does not freeze at 70°.

## SUMMARY

1. A study was made of the conditions of the diene synthesis of vinyl phenyl, vinyl cyclohexyl and vinyl n-hexyl ethers, and also of vinyl ethyl and vinyl phenyl sulfides with 2, 3-dimethyl-1, 3-butadiene. It was shown that in the above cases the diene synthesis is accompanied by the copolymerization of the 2, 3-dimethyl-1,3-butadiene with the given vinyl compounds.
2. Five adducts were isolated, being new derivatives of cyclohexene; they were characterized by their constants and by conversion to ethers of 3, 4-dimethyl-1-cyclohexanol.
3. It was found that under the investigated conditions the vinyl and thiovinyl ethers copolymerize with 2, 3-dimethyl-1, 3-butadiene up to the extent of 50 mole%.
4. It was observed that vinyl ethers containing cyclic radicals react most easily in the diene synthesis with 2, 3-dimethyl-1, 3-butadiene.

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# REACTION OF PRIMARY $\gamma$ -SILICON-CONTAINING ACETYLENIC ALCOHOLS WITH THIONYL CHLORIDE

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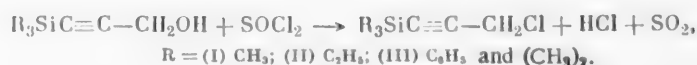
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 7,

pp. 2100-2102, July, 1961

Original article submitted July 27, 1960

The present investigation is a continuation of our studies [1] on the synthesis and transformations of various heteroorganic acetylenic alcohols and their derivatives. It seemed of interest to study the reaction of  $\gamma$ -silicon-containing acetylenic alcohols with thionyl chloride and establish if here the hydroxyl group is replaced by halogen or whether the starting alcohol is cleaved at the Si-C linkage.

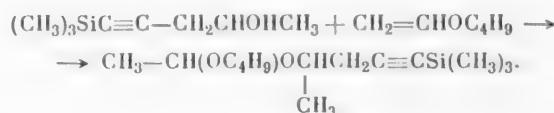
Investigation revealed that the reaction goes smoothly under comparatively mild conditions to yield the corresponding chlorides.



The yield of the  $\gamma$ -silicon-containing acetylenic chlorides reaches 90-95%. Next we investigated the reactivity of the obtained chlorides in the Grignard synthesis as exemplified by the following reaction:



and obtained the first member of the  $\gamma$ -silicon-containing acetylenic alcohols. That the hydroxyl group is present in the 5-(trimethylsilyl)-4-pentyn-2-ol was proved by synthesizing the organosilicon acetal, in accordance with the scheme:



## EXPERIMENTAL

The starting compounds had the following constants: 3-(trimethylsilyl)-2-propyn-1-ol, b.p. 61° (2 mm),  $n_D^{20}$  1.4523,  $d_4^{20}$  0.8806; 3-(triethylsilyl)-2-propyn-1-ol, b.p. 109-110° (6 mm),  $n_D^{20}$  1.4670,  $d_4^{20}$  0.8932; 3-(dimethylphenylsilyl)-2-propyn-1-ol, b.p. 131-132° (2 mm),  $n_D^{20}$  1.5335,  $d_4^{20}$  0.9996 [2].

(3-Chloropropynyl)-1-trimethylsilane (I). With stirring and cooling, 23.2 g of thionyl chloride was added in drops to a mixture of 17.5 g of 3-(trimethylsilyl)-2-propyn-1-ol and 1.5 g of pyridine. The reaction mixture was stirred for 2 hr and then allowed to stand overnight. The next day the mixture was stirred for another 3 hr at room temperature and then it was heated at 50-60° for 2-3 hr until the evolution of  $SO_2$  ceased. This was followed by the addition of 30 ml of water to decompose the unreacted thionyl chloride. The organic layer was separated from the aqueous layer, washed with water, dried over fused calcium chloride, and distilled. We isolated 18.5 g (92.5%) of the compound from the distillation.

b.p. 50° (17 mm),  $n_D^{20}$  1.4546,  $d_4^{20}$  0.9295,  $MR_D$  42.87, Calc. 42.77.  
Found %: Si 18.84,  $C_6H_{11}SiCl$ . Calculated %: Si 19.14.



(3-Chloropropynyl)-1-triethylsilane (II). The compound was synthesized in the same manner as described above. For reaction we took 8.51 g of 3-(triethylsilyl)-2-propyn-1-ol, 8.92 g of thionyl chloride and 1 g of pyridine. We isolated 8.95 g (95%) of the compound.

b.p. 72° (6 mm),  $n_D^{20}$  1.4698,  $d_4^{20}$  0.9262,  $MR_D$  57.03. Calc. 56.66.  
Found %: Si 15.16.  $C_9H_{17}SiCl$ . Calculated %: Si 14.84.

(3-Chloropropynyl)-1-dimethylphenylsilane (III). For reaction we took 10.15 g of 3-(dimethylphenylsilyl)-2-propyn-1-ol, 9.65 g of thionyl chloride and 1 g of pyridine. We obtained 9.9 g (90.5%) of the compound.

b.p. 118°C (6 mm),  $n_D^{20}$  1.5345,  $d_4^{20}$  1.0409,  $MR_D$  62.39. Calc. 62.44.  
Found %: Si 13.54.  $C_{11}H_{13}SiCl$ . Calculated %: Si 13.42.

5-(Trimethylsilyl)-4-pentyn-2-ol (IV). Into a three-necked, round-bottomed flask fitted with a reflux condenser, dropping funnel and a mechanical stirrer were charged 3.3 g of magnesium and 50 ml of absolute ether. Then, with stirring and slight warming, was added 2.5 g (from the total amount of 20 g) of (3-chloropropynyl)-1-trimethylsilane. When the reaction started, the remainder of the chloride was added in drops, along with 6 g of acetaldehyde and 20 ml of absolute ether. The reaction mixture was heated for 2-3 hr on the water bath with stirring and then allowed to stand overnight. The next day the mixture was heated another 1.5-2 hr, cooled in ice water, and treated with 5% hydrochloric acid until all of the precipitate had dissolved. The aqueous layer was separated from the ether layer and extracted 3-4 times with ether.

The ether layer and ether extracts were combined and washed with water, dried over fused potassium carbonate, the ether removed by distillation, and the residue was vacuum distilled. On distillation we collected 3.5 g (16.4%) of the compound.

b.p. 95-97° (2 mm),  $n_D^{20}$  1.4748;  $d_4^{20}$  0.9101.  
Found  $MR_D$  48.46. Calc. 48.74.  
Found %: Si 17.90.  $C_8H_{16}OSi$ . Calculated %: Si 17.9.

(4-Trimethylsilyl)-1-methyl-3-butyryl butyl acetal (V). With stirring, 2 drops of concd. hydrochloric acid was added to a mixture of 1.92 g of vinyl butyl ether and 3 g of 5-(trimethylsilyl)-4-pentyn-2-ol. Here the mixture warmed up to 26°. To complete the reaction, the mixture was heated at 60-70° for 2 hr and then allowed to stand overnight. The next day the reaction mixture was neutralized with fused potassium carbonate and then vacuum distilled. We isolated 4.68 g (97.5%) of the compound.

b.p. 153° (3 mm)  $n_D^{20}$  1.4655,  $d_4^{20}$  0.8925,  $MR_D$  79.12. Calc. 78.51.  
Found %: Si 11.52.  $C_{14}H_{26}O_2Si$ . Calculated %: Si 11.00.

#### SUMMARY

1. The reaction of primary  $\gamma$ -silicon-containing acetylenic alcohols with thionyl chloride was studied. A method was developed for obtaining organosilicon acetylenic chlorides of the propargyl type.
2. A method was proposed for obtaining secondary  $\gamma$ -silicon-containing acetylenic alcohols, based on the Grignard reaction of organosilicon acetylenic chlorides with aldehydes.
3. Five new organosilicon compounds were obtained and characterized: (3-chloropropynyl)-1-trimethylsilane, (3-chloropropynyl)-1-triethylsilane, (3-chloropropynyl)-1-dimethylphenylsilane, 5-(trimethylsilyl)-4-pentyn-2-ol, and (4-trimethylsilyl)-1-methyl-3-butyryl butyl acetal.

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FLUORINE - AND SULFUR - CONTAINING DERIVATIVES  
OF MESO - 3, 4 - DIPHENYLHEXANE

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In previous papers we described the synthesis of p,p'-dihydroxymeso-3,4-diphenylhexane (synestrol)(I) [1] and the dimethiodide of p,p'-bis-dimethylamino-meso-3,4-diphenylhexane (paramyon) (II) [2]. As is known, synestrol possesses estrogenic activity [3, 4], while paramyon has a curare-like action [4, 5]; both compounds are used in medical practice. The different character of the pharmacological action of these two compounds, depending on the nature of the substituents in the p- and p'-positions of meso-3, 4-diphenylhexane, caused us to synthesize a number of other meso-3, 4-diphenylhexane derivatives containing various groups as the R substituents.

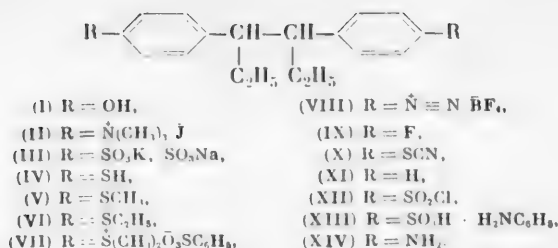
In the present paper we describe the sulfo derivatives of meso-3, 4-diphenylhexane (III) [5], the mercapto, methylmercapto, ethylmercapto and sulfonium derivatives (IV-VII), and also the bis-diazoborofluoride (VIII), difluoride (IX) and bis-thiocyanate (X) of meso-3, 4-diphenylhexane.

We used meso-3, 4-diphenylhexane (XI) [1] as the starting product for the synthesis of the indicated compounds. By reacting it with chlorosulfonic acid in dichloroethane medium we obtained the p,p'-disulfonyl chloride of meso-3, 4-diphenylhexane (XII), which was then converted to the dipotassium salt of p,p'-disulfo-meso-3, 4-diphenylhexane (III) [6]. This disulfonic acid was also characterized as the disodium salt (III) and as the aniline salt (XIII). Reaction of a water solution of either the dipotassium or the disodium salt of p,p'-disulfo-meso-3, 4-diphenylhexane with a water solution of barium chloride gave the barium salt, insoluble in both cold and hot water, while reaction with a water solution of calcium chloride gave the calcium salt, slightly soluble in either cold or hot water.

The p, p'-disulfonyl chloride of meso-3, 4-diphenylhexane was reduced to p, p'-bis-mercapto-meso-3, 4-diphenylhexane (IV), employing stannous chloride in HCl-saturated acetic acid solution according to the method given in [7] for the reduction of other sulfonyl chlorides. We isolated (IV) as a white precipitate. Hillmann-Elies, who obtained this compound by a different procedure [8], isolated it as an oil and did not subject it to further purification.

We obtained p,p'-bis-methylmercapto-meso-3, 4-diphenylhexane (V) by reacting (IV) in KOH solution with either methyl iodide or dimethyl sulfate. p,p' - Bis-ethylmercapto-meso-3, 4-diphenylhexane (VI) was obtained in a similar manner employing ethyl iodide. Alkylation of (V) with the methyl ester of benzenesulfonic acid gave the benzenesulfonic acid salt of the p,p'-bis-dimethylsulfonium derivative of meso-3, 4-diphenylhexane (VII).

In order to establish the position of the sulfur-containing substituents in the benzene rings of the synthesized meso-3, 4-diphenylhexane derivatives (III-VII, X and XII), we developed another method for obtaining p,p'-bis-mercapto-meso-3, 4-diphenylhexane (IV), starting with p,p'-diamino-meso-3, 4-diphenylhexane (XIV). The latter was subjected to diazotization, and the diazo product was isolated as the slightly water-soluble borofluoride (VIII), which was converted to the p,p'-bis-thiocyanate of meso-3, 4-diphenylhexane (X) by adding the borofluoride to an acetone solution of potassium and copper thiocyanates. Nitrogen was evolved here and (X) was obtained as a precipitate. Potassium thiocyanate facilitates the solution of copper thiocyanate in acetone. The copper thiocyanate was obtained by the procedure given in [9]. Employing  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ , the thus-obtained bis-thiocyanate (X) was reduced to p,p'-bis-mercapto-meso-3, 4-diphenylhexane (IV), which proved to be identical with the product obtained by the reduction of the p,p'-disulfonyl chloride of meso-3, 4-diphenylhexane (XII). p,p'-Difluoro-meso-3, 4-diphenylhexane was obtained by the thermal decomposition of the borofluoride (VIII). This product proved to be identical with the difluoride described in the literature [10], which was obtained by a different procedure.



The pharmacological testing of the synthesized compounds revealed that the p,p'-bis-dimethylsulfonium derivative of meso-3, 4-diphenylhexane (VII) possesses a high curare-like activity. The dipotassium salt of p,p'-disulfo-meso-3, 4-diphenylhexane (sigetin) (III) has been introduced into clinical practice. Sigetin can be used for the purpose of quieting the gonadotropic function of the pituitary [11], as a curative in asphyxia (suffocation) of the fetus [12], in disturbances of the ovarian-menstrual cycle [13], and for intensifying the muscular contractions of the uterus.

#### EXPERIMENTAL

**p,p'-Disulfonyl chloride of meso-3, 4-diphenylhexane (XII).** With stirring, 2 g of meso-3, 4-diphenylhexane (XI) was added at 17–20°, in 15 min, to a solution of 4.4 ml of chlorosulfonic acid in 15 ml of dry dichloroethane. The mixture was stirred at this temperature for another 3 hr, in which connection a precipitate began to deposit after about 35 min. Then the reaction mass was cooled in ice water and gradually treated with small pieces of ice, at a temperature not exceeding 25°. The precipitate was filtered, washed with water and then with dichloroethane. The air-dried precipitate (3.2 g) was recrystallized from 50 ml of dichloroethane using activated carbon. We obtained 2.5 g (68.3%) of a white compound, which began to change at 217°, and melted at 235–237°.

Found %: C 49.44, 49.41; H 4.77, 4.98; S 14.50, 14.73; Cl 15.71, 15.69.

$\text{C}_{18}\text{H}_{20}\text{O}_4\text{Cl}_2$ . Calculated %: C 49.65; H 4.63; S 14.73; Cl 16.29.

**Dipotassium salt of p,p'-disulfo-meso-3,4-diphenylhexane (III).** A solution of 3 g of KOH in 70 ml of water was heated under reflux for 5 hr with 5 g of the p,p'-disulfonyl chloride of meso-3, 4-diphenylhexane. The alkalinity of the medium was checked periodically using phenolphthalein as indicator. The slight excess of KOH was neutralized with dilute hydrochloric acid, and the cloudy solution was boiled with activated carbon and filtered hot. After 12 hr the precipitate was filtered, washed with water, and dried at 110°. We obtained 4.8 g (88%) of the salt. In the air the salt absorbs 2 moles of water in 24 hr, but it does not deliquesce here.

Found %: S 13.70, 13.77; K 16.31, 16.36.  $\text{C}_{18}\text{H}_{20}\text{O}_6\text{S}_2\text{K}_2$ . Calculated %: S 13.72;

K 16.47.

**Disodium salt of p,p'-disulfo-meso-3, 4-diphenylhexane (III).** This salt was obtained in the same manner as the K salt from a solution of 2 g of NaOH in 60 ml of water and 5 g of the p,p'-disulfonyl chloride of meso-3, 4-diphenylhexane. After drying at 110° the salt weighed 4.7 g (92.4%). In the air the salt absorbs 4 moles of water in 24 hr, but it does not deliquesce.

Found %: S 14.50, 14.42; Na 10.31, 10.38.  $\text{C}_{18}\text{H}_{20}\text{O}_6\text{S}_2\text{Na}_2$ . Calculated %: S 14.43;

Na 10.39.

**Dianiline salt of p,p'-disulfo-meso-3,4-diphenylhexane (XIII).** A solution of 0.5 g of the dipotassium salt of p,p'-disulfo-meso-3, 4-diphenylhexane in 30 ml of water was added to a solution of 0.3 ml of aniline and 0.5 ml of concd. hydrochloric acid in 5 ml of water. The obtained precipitate (0.5 g) was filtered and then recrystallized from 20 ml of water. We obtained 0.35 g (56.8%) of the salt as a white compound that decomposes at 322–326°.

Found %: N 4.54, 4.59; S 11.02, 11.06.  $\text{C}_{30}\text{H}_{36}\text{O}_6\text{N}_2\text{S}_2$ . Calculated %: N 4.80;

S 10.97.

**Borofluoride of p,p'-bis-diazo-meso-3,4-diphenylhexane (VIII).** A suspension of 4.7 g of p,p'-diamino-meso-3, 4-diphenylhexane (m.p. 140–142°) [1] in 90 ml of water and 9 ml of concd. hydrochloric acid was diazotized at 4–5° with a solution of 2.4 g of sodium nitrite in 25 ml of water. The mixture was stirred for 0.5 hr,

filtered from a small amount of deposit, and the filtrate was poured with stirring into an ice-cooled solution of 5 g of  $\text{NaBF}_4$  in 12 ml of water. The mixture of liquid and precipitate was stirred for 0.5 hr, after which the precipitate was filtered, washed with a little water, and then several times with ether. We obtained 7.8 g (95.4%) of the borofluoride (VIII) as a white compound with a creamish tinge.

Found %: N 12.44, 12.21.  $\text{C}_{18}\text{H}_{20}\text{N}_4\text{B}_2\text{F}_8$ . Calculated %: N 12.24.

p,p'-Difluoro-meso-3, 4-diphenylhexane (IX). Using an air reflux condenser, 1.5 g of the borofluoride (VIII) was heated for 0.5 hr at 120–130° in an oil bath. After cooling, the solid residue was dissolved with heating in 10 ml of alcohol and the solution was poured with stirring into a solution of 0.6 g of KOH in 75 ml of water. After 1 hr the precipitate was filtered, washed with water, and recrystallized from dilute acetic acid using activated carbon. We obtained 0.55 g of the compound as a white substance with m.p. 98–100°. The filtrate was heated to the boil, 5 ml of water was added, and an additional 0.1 g of the substance was obtained when the clear hot solution was cooled. Total yield 73.6%.

Found %: C 78.80, 78.88; H 7.67, 7.67.  $\text{C}_{18}\text{H}_{20}\text{F}_2$ . Calculated %: C 78.80; H 7.71.

p,p'-Bis-thiocyanato-meso-3, 4-diphenylhexane (X). With stirring, 2.3 g of the borofluoride (VIII) was added at 20–33°, in 20 min, to a mixture of 30 ml of acetone, 1.5 g of KSCN and 1.5 g of CuSCN. The addition of each portion of the borofluoride caused the immediate evolution of nitrogen. After stirring for 20 min, the white precipitate (1.6 g) was filtered, while the red filtrate was distilled to remove all of the acetone, and the residue was stirred at room temperature for 1 hr with 30 ml of anhydrous benzene, after which the residual yellow precipitate (2 g) was filtered. The benzene filtrate was distilled to remove the benzene and the residue was recrystallized from 75 ml of petroleum ether. We obtained 1.4 g (81.1%) of lemon-colored (X), m.p. 122–124°.

Found %: C 68.12, 68.20; H 5.87, 5.97; N 7.93, 7.80; S 18.34, 18.20.  $\text{C}_{20}\text{H}_{20}\text{N}_2\text{S}_2$ . Calculated %: C 68.14; H 5.72; N 7.95; S 18.19.

p,p'-Bis-mercapto-meso-3, 4-diphenylhexane (IV). Method A. Hydrogen chloride was passed into a mixture of 100 g of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  in 400 ml of acetic acid until the precipitate dissolved. The warm solution was heated to 80° and then with stirring 7.8 g of the p,p'-disulfonyl chloride of meso-3, 4-diphenylhexane was added in several minutes. The mixture was stirred for 45 min and then 270 ml of concd. hydrochloric acid was added to the hot solution. After cooling, the precipitate was filtered, washed with a mixture of acetic and hydrochloric acids, then with hydrochloric acid and finally with water, after which it was stirred for 1 hour with a solution of 5 g of KOH in 200 ml of water and the filtered solution was poured into 100 ml of concd. hydrochloric acid. The obtained precipitate was filtered, washed with hydrochloric acid and then with water, after which it was dried at 60° and recrystallized from 160 ml of alcohol. We obtained 3.3 g of (IV), m.p. 155–157°. Evaporation of the mother liquor to a volume of about 50 ml gave an additional 0.7 g of the substance. The total yield of the substance was 4 g (73.8%). The compound is soluble in hot petroleum ether.

Found %: C 71.53, 71.63; H 7.42, 7.32; S 20.87, 20.98.  $\text{C}_{18}\text{H}_{22}\text{S}_2$ . Calculated %: C 71.47, H 7.33; S 21.13.

Method B. A mixture of 10 g of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  and 40 ml of acetic acid was saturated with hydrogen chloride until all of the  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  had dissolved, after which 0.6 g of p,p'-bis-thiocyanato-meso-3, 4-diphenylhexane was added in portions at 80°, with stirring. The mixture was stirred for 45 min at 80° and then was worked up as described in A. After purification using KOH solution, the precipitate was recrystallized from 15 ml of alcohol. We obtained 0.35 g (68.0%) of (IV), m.p. 155–157°. The mixed melting point with the precipitate obtained by method A was not depressed.

p, p' -Bis-methylmercapto-meso-3, 4-diphenylhexane (V). With shaking, 0.7 ml of methyl iodide or 0.8 ml of dimethyl sulfate was added gradually to a solution of 0.6 g of KOH in 20 ml of water and 1 g of p,p'-bis-mercapto-meso-3, 4-diphenylhexane. The mixture was stirred for 40 min at room temperature and for 40 min at 35–40° (in the reaction mass). After cooling, the white precipitate was filtered, washed with water, and recrystallized from 100 ml of alcohol. We obtained 1.05 g (96.1%) of canary-colored (V), m.p. 150–152°.

Found %: C 72.65, 72.53; H 7.97, 7.71; S 19.47, 19.40.  $\text{C}_{20}\text{H}_{26}\text{S}_2$ . Calculated %: C 72.67; H 7.93; S 19.40.

p,p'-Bis-ethylmercapto-meso-3, 4-diphenylhexane (VI). In the same manner as described above, the treatment of 1.5 g of (IV) in a solution of 0.9 g of KOH plus 20 ml of water with 0.9 g of ethyl iodide gave 1.75 g of a white precipitate, from which after recrystallization from 20 ml of alcohol we obtained 1.5 g (84.3%) of canary-colored (VI), m.p. 96–98°.

Found %: C 73.99, 73.97; H 8.40, 8.34; S 17.77, 17.60,  $C_{22}H_{20}S_2$ . Calculated %: C 73.68; H 8.04; S 17.89.

Di(methyl benzenesulfonate) of p,p'-bis-methylmercapto-meso-3, 4-diphenylhexane (VII). Using an air reflux condenser, a mixture of 4.9 g of p, p'-bis-methylmercapto-meso 3, 4-diphenylhexane and 20 ml of methyl benzenesulfonate was heated for 1.5 hr at 135–150° in an oil bath. After cooling, the solid residue was treated with 40 ml of dry acetone and the mixture was cooled in a cooling mixture for 24 hr. The precipitate was filtered (8.4 g). Dilution of the filtrate with 50 ml of absolute ether gave an additional 1.7 g of precipitate. The precipitate (8.4 g) was recrystallized from aqueous acetone (20 ml of water and 75 ml of acetone) using activated carbon. The filtrate was cooled for 12 hr in a cooling mixture and the obtained precipitate was filtered and dried at 80°. We obtained 5.4 g of (VII) as a white product. M.p. 188–190° (with decompn.). Evaporation of the filtrate in vacuo on the water bath and treatment of the residue with acetone gave an additional 1.5 g of substance. The total yield was 6.9 g (68.9%).

Found %: S 18.72, 18.91.  $C_{34}H_{42}O_6S_4$ . Calculated %: S 19.00.

#### SUMMARY

1. A number of fluorine - and sulfur-containing derivatives of meso-3, 4-diphenylhexane were synthesized.
2. p,p'-Bis-mercapto-meso-3, 4-diphenylhexane was obtained by two methods: by the reduction of the p,p'-disulfonyl chloride of meso-3, 4-diphenylhexane and by the conversion of p,p'-diamino-meso-3, 4-diphenylhexane to the bis-diazoborofluoride, with subsequent conversion of the borofluoride to the bis-thiocyanate, which was reduced to the bis-mercapto derivative.
3. The synthesized derivatives were found to contain some pharmacologically active compounds. One of these compounds—the dipotassium salt of p,p'-disulfo-meso-3, 4-diphenylhexane (sigetin)—is being used in clinical practice.

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# STUDIES OF ADENOSINE - 2' - PHOSPHOAMINO ACID DERIVATIVES

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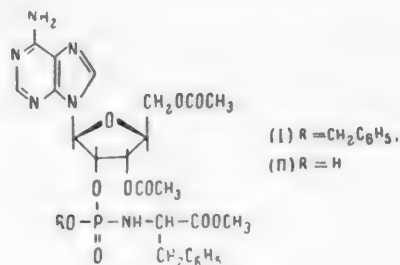
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Recently there has been an intensive development of the chemistry of amino acid derivatives of the nucleotides. Particular attention has been devoted to study of nucleoside phosphoamino acid derivatives, that is, compounds in which there are phosphoamide bonds between the phosphoryl group of the nucleotide and the amino group of the amino acid. One of the reasons for the interest of investigators in these compounds is the hypothesis of the possibility of the participation of such structures in the process of biosynthesis of proteins [1]. It has recently been shown that adenosine-5'-phosphoamino acid derivatives can share in peptide formation in vitro [2]. In this connection there is interest in studying the possibility of participation in peptide synthesis of the corresponding adenosine-2'-phosphoamino acid derivatives. An account of the results of this investigation is the subject of the present paper.

As the object of study we chose the methyl ester of N-(3',5'-di-acetyladenosine-2'-benzylphospho)-D,L-phenylalanine (I) and N-(3',5'-diacetyladenosine-2'-phospho)-D,L-phenylalanine (II).

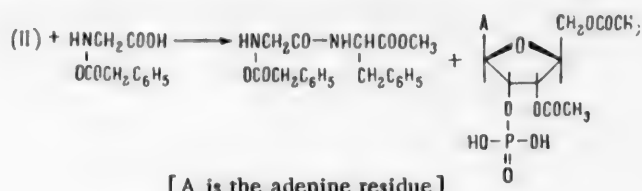


The synthesis of compound (I) was worked out previously [3]. To obtain compound (II) we used catalytic hydrogenolysis of (I) leading to selective splitting of the benzyl group at the phosphoester bond. The optimum result was obtained by 50-minute hydrogenation of compound (I). The isolated substance was then further purified by preparative paper chromatography. Compound (II) obtained in this way was a colorless, amorphous, very hygroscopic substance which quickly deliquesced in air. The structure of compound (II) follows from its synthesis and was confirmed by the results of hydrolysis and also by its ultraviolet absorption spectrum. A characteristic peculiarity of compound (II) is its extreme instability. The strength of the phosphoamide bond in this compound is sharply decreased compared to compound (I), and substance (II) shows gradual splitting even when kept at room temperature without access of moisture.\*

It is known from the chemistry of the amidophosphoric acids that the strength of the phosphoamide bond is decreased on going from the substituted amides of diesters of phosphoric acid to the amide of the monoester of phosphoric acid, and finally, to the nonesterified amidophosphoric acid. Therefore, it is not remarkable that compound (II), which is a substituted amide of a monoester of phosphoric acid, is less stable than compound (I) which from this point of view is a substituted amide of a diester of phosphoric acid.

\* In this connection, in all the following experiments we used freshly prepared samples of compound (II).

Further experiments established that compound (II) could react with cbz-amino acids,\* leading to the formation of a dipeptide. Thus, when a mixture of compound (II) with cbz-glycine was boiled in dioxane, there was formation of the corresponding dipeptide, the methyl ester of cbz-glycyl-D,L-phenylalanine, which was detected chromatographically after removing the cbz-group by catalytic hydrogenation. The formation of the dipeptide was also shown by detection of the corresponding amino acids (glycine and phenylalanine) in the acid hydrolyzate of the dipeptide eluate. In an analogous way we established the formation of a dipeptide also by reaction of compound (II) with cbz-glycine in dioxane at 37°. The formation of the dipeptide could be shown by the following summarized scheme:



At the same time it was established that the reaction of free methyl ester of phenylalanine with cbz-glycine also led to the formation of a dipeptide. Dioxane was not a specific medium for this reaction, and could be replaced by other nonpolar solvents, for example, toluene. The resulting dipeptide could not only be detected chromatographically, but could also be isolated preparatively. From the theoretical point of view the formation of a dipeptide under these conditions is not unexpected, for the principle is well known of the possibility of acylating primary amines by carboxylic acids, as actually occurs in this case.

On the basis of our suggestion we propose that the reaction of compound (II) with cbz-glycine can occur by a two stage mechanism, the first step of which consists in the splitting of (II) with formation of free methyl ester of phenylalanine, and the second step in the acylation of this ester by cbz-glycine. For the initiation of the process it is evidently sufficient that there be present merely a slight trace of moisture, and then the water needed for occurrence of the first step will be continuously generated by the second step of the process.

It should be noted that compound (I), in which the phosphoamide bond is much more stable, did not show formation of a dipeptide in any of the analogous experiments. In the same way we did not find the formation of a dipeptide in the reaction of compound (II) with free glycine. These facts confirm the idea of the two stage mechanism of the reaction and are fully comprehensible from this point of view, since in the first case there is no splitting of the methyl ester of phenylalanine, and in the second, the acylating agent is absent since glycine does not exist as a carboxylic acid, but as an inner salt.

#### EXPERIMENTAL

**Paper distributive chromatography.** For chromatography we used "Chromatographic B" paper from the Volodarskii Leningrad Factory. We used the following solvent systems: n-butyl alcohol-water-acetic acid (4:5:1) (system 1); n-butyl alcohol saturated with water (system 2); isoamyl alcohol-5% Na<sub>2</sub>HPO<sub>4</sub> (both phases [4]) (system 3); n-butyl alcohol saturated with 5% ammonium hydroxide (system 4). The substances were detected on the chromatogram by absorption of ultraviolet light [5], and also with molybdate [6] and benzidine reagents [7]. Compounds with a free  $\alpha$ -aminogroup were detected with ninhydrin. The R<sub>f</sub> values given later refer to an ascending chromatogram. When the R<sub>f</sub> values are not given, the substance was identified on the chromatogram by direct comparison with a commercial sample.

**Study of hydrogenolysis of the methyl ester of N-(3',5'-diacetyl-adenosine-2'-benzylphospho)-D, L-phenylalanine (I) with time.** Thirty mg of compound (I) [3] was dissolved in 50 ml of 50% aqueous methanol, 30 mg of palladium oxide was added and the mixture was hydrogenated at normal pressure and room temperature with shaking. Samples were withdrawn periodically and were chromatographed with system 1. In the 40-minute sample we detected: starting substance (I) (R<sub>f</sub> 0.90 in ultraviolet) and compound (II) (R<sub>f</sub> 0.74 in ultraviolet). In the 50-minute sample we detected: starting substance (I) (weak spot) and compound (II) (intense spot with R<sub>f</sub> 0.74). In the 60-minute sample we found: starting substance (I) (weak spot), compound (II) (R<sub>f</sub> 0.74 in the ultraviolet), methyl ester of phenylalanine (ninhydrin, R<sub>f</sub> 0.59) and yeast adenylic acid (R<sub>f</sub> 0.15, in ultraviolet and molybdate reagent).

\* cbz = carbobenzoxy - (C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>OCO-).



Methyl ester of N- (3',5'-diacetyladenosine-2'-phospho)-D,L-phenylalanine (II). We dissolved 0.1 g of compound (I) in 100 ml of 50% aqueous methanol, added 30 mg of palladium oxide, and hydrogenated the mixture at atmospheric pressure and room temperature for 50 minutes with shaking. Then the catalyst was filtered off, the water-methanol filtrate was evaporated in a vacuum, traces of water were removed by azeotropic distillation with benzene, the residue was dissolved in 2 ml of dry chloroform and this solution was added dropwise to 100 ml of cooled ligroin (b.p. 70-90°). The precipitating colorless, amorphous substance was separated by decantation; after repeated reprecipitations from chloroform by ligroin we obtained 80 mg of a colorless, amorphous, hygroscopic substance. Chromatography in system 1 showed that this substance had  $R_f$  0.74 (appearance in the ultraviolet), but contained an admixture of the starting substance (I) ( $R_f$  0.90 in ultraviolet). To obtain chromatographically pure (II), the isolated substance was dissolved in methanol, the solution was placed as a band on a sheet of chromatograph paper and was chromatographed in system 1. After the appearance in the ultraviolet of the corresponding zone, the chromatogram was eluted with 20 ml of ethanol, the eluate was evaporated dry in a vacuum (at a temperature not above 30°), and we obtained a colorless, amorphous substance with m.p. 64° which quickly deliquesced in air.

Chromatographic characteristics:  $R_f$  0.74 (in system 1), 0.30 (in system 2), 0.60 (in system 3). Absorption in the ultraviolet:  $\lambda_{\max}$  260 m $\mu$ ;  $\epsilon_{\max}$  12900 (96% ethanol).

Found %: C 47.47; H 5.49; P 4.46.  $C_{24}H_{29}O_{10}N_6P \cdot H_2O$ . Calculated %: C 47.23; H 5.11; P 5.08.

Splitting of compound (II) when kept. Chromatographically pure samples of compound (II), prepared as described above, were placed in a desiccator with phosphorus pentoxide and kept for three days at room temperature. Then they were chromatographed in systems 1 and 3. Along with unchanged compound (II) we noted 3', 5'-diacetyladenosine-2'-phosphate ( $R_f$  0.33, system 1 in ultraviolet), adenosine-2'-phosphate ( $R_f$  0.69, system 3, in ultraviolet and molybdate) and the methyl ester of phenylalanine ( $R_f$  0.59, system 1, ninhydrin).

Hydrolysis of compound (II). Three mg of (II) was dissolved in 0.1 ml of ethanol, 0.4 ml of 1 N sulfuric acid was added, and the solution was kept in the thermostat at 37°. After 1, 15, 30 and 60 minutes we took samples which were chromatographed in systems 1 and 3. In the hydrolyzate we found adenosine-2'- and -3'-phosphoric acid (in system 3,  $R_f$  0.69 and 0.62, respectively), the methyl ester of phenylalanine ( $R_f$  0.59 in system 1) and phenylalanine ( $R_f$  0.52 in system 1).

Reaction of compound (II) with cbz-glycine. a) In boiling dioxane. Forty mg of compound (II) and 50 mg of cbz-glycine were dissolved in 50 ml of dry dioxane and the solution was boiled for two hours with protection from moisture. After cooling, the dioxane was distilled off in a vacuum, the remaining oil was dissolved in 50 ml of chloroform, and washed with 0.1 N hydrochloric acid, 0.1 N sodium hydroxide and water. After the solution had been dried with ignited sodium sulfate, the chloroform was distilled off, the residue was dissolved in 20 ml of methanol, 10 mg of palladium oxide was added, and hydrogenation was carried out for five hours at room temperature and atmospheric pressure to remove the cbz-group. After removal of the catalyst, the methanol solution was evaporated off to a volume of 1 ml, and was chromatographed in system 2 using as the standard a commercial sample of the methyl ester of glycyl-D,L-phenylalanine. Using ninhydrin, we detected this dipeptide ester in the reaction mixture ( $R_f$  0.37). The corresponding zone of a chromatogram not treated with ninhydrin was eluted with 10 ml of methanol for two hours at 37°, the eluate was evaporated dry, and the residue was boiled for five hours with 2 ml of 6 N hydrochloric acid. In the hydrolyzate we detected chromatographically (in system 1) glycine and phenylalanine.

b) In dioxane at 37°. Twenty mg of compound (II) and 25 mg of cbz-glycine were dissolved in 25 ml of dry dioxane and left in a thermostat at 37° for 12 hours. Then the solution was evaporated in a vacuum, the residue was dissolved in 25 ml of chloroform, and the chloroform solution was treated as described in the previous experiment. Chromatography in system 2 showed the methyl ester of glycyl-D,L-phenylalanine. The amino acid composition was shown after hydrolysis by 6 N hydrochloric acid as described above.

Reaction of methyl ester of D, L-phenylalanine with cbz-glycine. a) In boiling dioxane. A solution of 0.45 g of methyl ester of D, L-phenylalanine and 0.55 g of cbz-glycine in 30 ml of dry dioxane was boiled for two hours with protection from moisture; then the solution was evaporated in a vacuum, the residual oil was dissolved in 50 ml of chloroform, washed with 0.1 N hydrochloric acid, 0.1 N sodium hydroxide and water, dried with ignited magnesium sulfate, and evaporated in a vacuum. The residue was dissolved in 50 ml of methanol and the cbz-group was removed by catalytic hydrogenation as described above. Chromatography in the system 2 showed the methyl ester of glycyl-D, L-phenylalanine ( $R_f$  0.37). A corresponding portion of the chromatogram not submitted to ninhydrin

was eluted and hydrolyzed with 6 N hydrochloric acid as described above. Chromatography in system 2 showed glycine and phenylalanine in the acid hydrolyzate.

b) In boiling toluene. The experiment was carried out analogously to the previous one, replacing the dioxane by toluene. Chromatography and later acid hydrolysis showed the formation of the methyl ester of cbz-glycyl-D, L-phenylalanine.

c) In dioxane at 37°. The experiment was carried out in the same way as in case "a" but at 37°. The reaction was kept at this temperature for 24 hours. Formation of the methyl ester of cbz-glycyl-D, L-phenylalanine was shown chromatographically and by later acid hydrolysis as described above.

d) Preparative experiment in boiling dioxane. A solution of 2.85 g of the methyl ester of D, L-phenylalanine and 3.3 g of cbz-glycine in 60 ml of dry dioxane was boiled for three hours with protection from moisture; then the dioxane was distilled off in a vacuum, the remaining oil was dissolved in 60 ml of chloroform which was washed with 1 N hydrochloric acid, with water, with a 3% aqueous solution of sodium bicarbonate, again with water, and was dried with ignited sodium sulfate. The flaky precipitate which separated from the chloroform solution on standing was separated, washed with chloroform, and was identified as 3, 6-dibenzyl-2, 5-diketopiperazine (chromatographically in systems 1, 2, and 4; developed with benzidine).

The wash chloroform was combined with the filtrate, the combined solutions were evaporated in a vacuum, the residue, a mixture of oily and crystalline substances, was treated with methanol and the crystalline substance insoluble in methanol was identified chromatographically and by the m.p. (m.p. 290°) as 3, 6-dibenzyl-2, 5-diketopiperazine. The methanol extracts were combined, evaporated in a vacuum, the remaining oil was dried by distillation with benzene, and was crystallized by grinding with 50 ml of absolute ether. We obtained 200 mg of the methyl ester of cbz-glycyl-D, L-phenylalanine in the form of a colorless, finely crystalline substance with m.p. 78°. A mixed sample with a commercial form [8] gave no melting point depression. According to chromatographic characteristics ( $R_f$  0.90 in system 1, 0.84 in system 2, 0.98 in system 4) and ultraviolet absorption in 96% ethanol ( $\lambda_{max}$  260m $\mu$ ;  $\epsilon_{max}$  480), this substance also does not differ from commercial methyl ester of cbz-glycyl-D, L-phenylalanine.

Study of the reaction of compound (I) with cbz-glycine. a) In dioxane at 37°. A solution of 20 mg of compound (I) and 50 mg of cbz-glycine in 50 ml of dry dioxane was kept for 12 hours in a thermostat at 37°. Further treatment was carried out as described above in the experiment on reaction of compound (II) with cbz-glycine. After chromatography in system 2, no dipeptide was found.

b) In boiling dioxane. A solution of 20 mg of compound (I) and 50 mg of cbz-glycine in 50 ml of dry dioxane was boiled for two hours with protection from moisture. Further treatment was carried out as described above, corresponding to the experiment with compound (II). After chromatography in system 2, no dipeptide was found.

Study of the reaction of compound (II) with glycine. Twenty mg of compound (II) and 25 mg of cbz-glycine were dissolved in 25 ml of dry dioxane and the solution was kept at 37°C for 24 hours. Then the solution was treated as described above. After chromatography in system 2, no dipeptide was found.

#### SUMMARY

1. Catalytic hydrogenolysis of methyl ester of N-(3',5'-diacetyladenosine-2'-benzylphospho)-D, L-phenylalanine gave the methyl ester of N-(3',5'-diacetyladenosine-2'-phospho)-D, L-phenylalanine. It was shown that the reaction of the latter with cbz-glycine led to formation of the methyl ester of cbz-glycine D, L-phenylalanine.
2. It was shown that this dipeptide is formed under the same conditions in the reaction of cbz-glycine with commercial methyl ester of D, L-phenylalanine.
3. We have suggested a mechanism for peptide formation with participation of N-(3',5'-diacetyladenosine-2'-phospho)-D, L-phenylalanine.

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# CYCLOPHOSPHATE FORMATION IN THE ADENOSINE-2'- PHOSPHOAMIDE SERIES

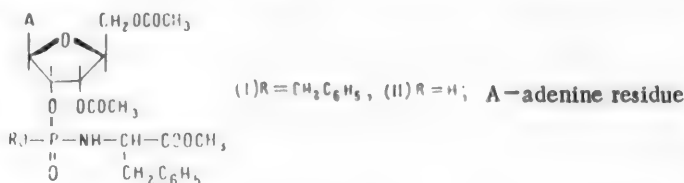
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The idea of intermediate formation of nucleoside-2',3'-cyclophosphates in the splitting of polyribonucleotides is now generally accepted [1]. However, the question of whether such cyclophosphate structures can be formed in the hydrolysis of nucleosidephosphoamino acid derivatives has not yet been studied, although the extent of this reaction could be of great help in studying the chemical structure of the natural nucleotide-amino acid formation and in the interpretation of very important biochemical processes on a molecular level.

In this connection, we have considered it interesting to study the possibility of cyclophosphate formation in the alkaline hydrolysis of such nucleoside phosphoamino acid derivatives as would have phosphoamido bonds in the cis-glycol part of the ribonucleoside.

As objects of study we chose the methyl esters of N-(3',5'-diacetyladenosine-2'-benzylphospho)-D, L-phenylalanine (I) [2], and N-(3',5'-dicaetyladenosine-2'-phospho)-D, L-phenylalanine (II) [3], which are approximate models of nucleoside phosphoamides in the middle of a polynucleotide chain and at its end, respectively.



In our opinion, these compounds are suitable models also for an experimental test of the hypothesis of the blocking of cyclophosphate formation in nucleoside phosphoamides as recently suggested by American investigators [4]. Although in compounds (I) and (II) the cis-hydroxyls are acetylated, this cannot affect the nature of the process, since in an alkaline medium the acetyl groups are quickly removed [5-8]. With other conditions equal, this fact can only make the process of cyclophosphate formation difficult, but cannot facilitate it in the least. The fact that in compounds (I) and (II) the phosphoamide bond is formed on  $C_2'$  and not on  $C_3'$  also cannot have any significance in principle for testing this hypothesis, for it is known that cyclophosphates are formed with equal success from nucleoside-3'- and nucleoside-2'-phosphates.

For a study of the products of alkaline hydrolysis we used distributive chromatography in a two-phase Carter system [9]. Using this method we established that on alkaline hydrolysis of compound (I) there was formed an equimolecular mixture of 2'- and 3'- phosphates of adenosine. This result showed with certainty the intermediate formation in the alkaline hydrolysis of (I) of an adenosine-2',3'-cyclo-phosphate structure, since in the opposite case we would expect the formation of the 2'-isomer only.

The alkaline hydrolysis of compound (II) also led to formation of a mixture of 2'- and 3'-phosphates of adenosine, but the ultraviolet spectrophotometric treatment of the corresponding eluates showed that the amount of these isomers was 3:1. If we consider the lower stability of the phosphoamide bond in compound (II) [3], this fact becomes fully comprehensible and permits us to assume that the alkaline hydrolysis of (II) occurs in two directions at the same time: with intermediate formation of a cyclophosphate structure and with direct splitting of the P-N bond.

These results lead to the conclusion that the hypothesis of blocking cyclophosphate formation in the nucleoside phosphoamides [4] is not confirmed in experimental tests on models. Hence, there is no reason to consider that in the polyribonucleotide chain with a phosphoamide bond in a definite portion there will be destruction of cyclophosphate formation and the corresponding internucleotide bonds will be stabilized to alkaline hydrolysis. On the contrary, we can expect that these polynucleotides will undergo the ordinary alkaline hydrolysis entirely without excluding the internucleotide bonds.

As applied to a strong nucleotide-amino acid complex [4], this conclusion means that if in this complex there is actually realized a phosphoamide bond, then it is unlikely that this bond will occur on the phosphorus atom next to which is the free *cis*-hydroxyl. In other words, it is unlikely that there will be a strong phosphoamide bond on the phosphorus atom which takes part in the formation of the normal 3',5'-internucleotide bond or similar bonds of any other type except the unusual 5',5'-internucleotide bond.

#### EXPERIMENTAL

**Distributive paper chromatography.** We used "Chromatographic B" paper of the Volodarskii Leningrad Factory. We used the following systems of solvents: *n*-butyl alcohol-water-acetic acid (4:5:1) (system 1); isoamyl alcohol-5%  $\text{Na}_2\text{HPO}_4$  (system 2). The substance was developed on the chromatogram with the Brumberg ultrachemscope [10]. Phenylalanine was developed with ninhydrin. The values for  $R_f$  given below refer to an ascending chromatogram. Identification of substances on the chromatogram was carried out by direct comparison with known samples.

**Alkaline hydrolysis of compound (I).** Five mg of (I) [2] was dissolved in 0.2 ml of ethanol, 0.4 ml of 1 N sodium hydroxide was added, and the solution was placed in a thermostat regulated at 37°. After 1, 15, 30 and 60 minutes, samples were withdrawn and were chromatographed in systems 1 and 2. Starting substance (I) was absent even after 1-minute hydrolysis. In all the samples, including the one-minute one, we observed adenosine-2'-phosphoric and adenosine-3'-phosphoric acids (in system 2,  $R_f$  0.69 and 0.62, respectively), and also phenylalanine ( $R_f$  0.52 in system 1) and adenosine ( $R_f$  0.44 in system 1). After development of the part of the chromatogram which corresponded to adenosine-2'- and adenosine-3'-phosphoric acids, it was cut out, eluted with 0.1 N sodium hydroxide, and the eluate was submitted to spectrophotometry at 260 m $\mu$ . For the ratio of optical densities of the solutions we obtained  $D_{260}^{2'}:D_{260}^{3'} = 1:1$ .

**Alkaline hydrolysis of compound (II).** Three mg of chromatographically pure (II) obtained as described previously [3] was dissolved in 0.1 ml of ethanol, 0.4 ml of 1 N sodium hydroxide was added, and the solution was kept in the thermostat at 37°. After 1, 15, 30, 45 and 60 minutes we took samples which were chromatographed in systems 1 and 2. The starting substance (II) disappeared even in the 1-minute sample. In all the samples, including the one-minute one, we noted adenosine-2'-phosphoric acid ( $R_f$  0.69 in system 2), adenosine-3'-phosphoric acid ( $R_f$  0.62 in system 2), adenosine ( $R_f$  0.44 in system 1) and phenylalanine ( $R_f$  0.52 in system 1).

For determination of the relative amounts of adenosine-2'-phosphoric and adenosine-3'-phosphoric acids, the corresponding parts of the chromatogram obtained in system 2 were cut out, eluted with 5 ml of 0.1 N sodium hydroxide for two hours at 37°, after which the eluates were submitted to spectrophotometry at wave length 260 m $\mu$ . For the ratio of optical densities of the solutions we obtained  $D_{260}^{2'}:D_{260}^{3'} \approx 3:1$ .

#### SUMMARY

1. We have established that alkaline hydrolysis of the methyl esters of *N*-(3',5'-diacetyladenosine-2'-benzylphospho)-D,L-phenylalanine and *N*-(3',5'-diacetyladenosine-2'-phospho)-D,L-phenylalanine takes place through a stage of intermediate formation of an adenosine-2', 3'-cyclophosphate structure. In the case of *N*-(3',5'-diacetyladenosine-2'-phospho)-D,L-phenylalanine there is also direct splitting of the P-N bond.
2. We have shown that the hypothesis of blocking of cyclophosphate formation in nucleoside phosphoamides in an experimental test on models is not confirmed. In this connection we have discussed the possibility of a type of phosphoamide bond in strong nucleotide-amino acid complexes.

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## AMINOSULFIDES AND AMINOSULFONES

### XIX. ADDITION OF o- AND p-NITROPHENYLMERCAPTANS

#### TO $\alpha, \beta$ -UNSATURATED COMPOUNDS \*

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It is known that mercaptans easily add to  $\alpha, \beta$ -unsaturated compounds in the presence of catalysts with a basic character [1-5]. In the present investigation we have studied the reaction of addition of o- and p-nitrophenylmercaptans to acrylonitrile,  $\alpha$ -chloro- and  $\alpha$ -bromoacrylonitriles, and methylacrylate in the presence of triethylamine and pyridine. As a result we obtained the corresponding sulfides  $ArSCH_2CHXR$  (I-IV). When the sulfides (I, II, IV) were heated with concentrated or dilute hydrochloric acid, they easily were hydrolyzed to the corresponding acid (V-VII) (Table 2). It should be noted that the introduction of halogen into the molecule of sulfide (II, III) makes the saponification to acid difficult. Sulfides (I-IV) were oxidized to the sulfones (VIII-XI) by hydrogen peroxide in glacial acetic acid [6, 7] (Table 3).

Sulfones which contain the nitrile groups are easily hydrolyzed in acid medium to acids (XII-XIV) (Table 4).

It was established experimentally that halogen in sulfides (II, III) does not enter the reaction of nucleophilic substitution with semicarbazide, thiosemicarbazide and potassium thiocyanate. Attempts to carry out this reaction with sulfone (X) also failed to give the expected result. In this case we obtained a sulfone which did not contain halogen and which decolorized a solution of potassium permanganate well. As investigation confirmed, this unsaturated sulfone evidently was formed as a result of dehydrohalogenation of the starting halosulfone (X) and had the structure  $p-NO_2C_6H_4SO_2CH=CH-CN$  (XVI). None of the sulfides or sulfones which we synthesized have been described in the literature.

#### EXPERIMENTAL

Aryl- $\beta$ -cyanoethylsulfides (I-IV). The reaction of o- and p-nitrophenylmercaptan with acrylonitrile and with  $\alpha$ -haloacrylonitrile was carried out in the presence of triethylamine in an atmosphere of nitrogen. To 2 g of freshly prepared o- or p-nitrophenylmercaptans [7] was added 2 drops of triethylamine and 1.5 ml of acrylonitrile stabilized with hydroquinone. The reaction mass was cooled to 20-25° and kept at room temperature for 6-8 hours in a nitrogen atmosphere. At the end of this time the precipitate was filtered off and washed with alcohol and ether. The resulting sulfide after two crystallizations from 50% alcohol appeared as needle-shaped crystals with a yellow color, soluble in acetone and dioxane, but insoluble in water (Table 1).

The reaction of  $\alpha$ -chloro- and  $\alpha$ -bromoacrylonitrile [9] with p-nitrophenylmercaptan was carried out at 30-40° in the course of 1-1.5 hours, after which the reaction mass stood for 12-15 hours at room temperature. The sulfides which formed were separated and purified by the process described above.

Aryl- $\beta$ -carboxyethylsulfides (V-VII). Substances (I, II, IV) were saponified with concentrated or dilute (1:1) hydrochloric acid. Two g of sulfide and 20 ml of 37% hydrochloric acid were mixed at 70°. After 4-5 hours saponification, the reaction mixture was treated with 10 ml of water; the crystals which precipitated were filtered off and washed, first with cold water (to negative reaction for the chlorine ion), and then with alcohol. After two crystallizations from water, the crystalline substance separated with an individual melting point. All of them were easily soluble in dioxane, in hot alcohol and water, and were not soluble in benzene or benzene (Table 2).

Aryl- $\beta$ -cyanoethylsulfones (VIII-XI). Oxidation of the sulfides (I-IV) was carried out with 30% hydrogen peroxide solution. To the sulfide dissolved in glacial acetic acid with mechanical stirring was added simultaneously acetic anhydride in an amount required to bind the water which was evolved in the reaction and present in the

\* Communications XII-XVIII: see Proceedings of the Leningrad Chemical-Pharmaceutical Institute, No. 11 [in Russian] (1961).

TABLE 1  
Aryl- $\beta$ -cyanoethylsulfides, ArSCH<sub>2</sub>CHXCN

Com- pound No.	Name	M. p.	Yield, %	Empirical formu- la	Found, %				Calculated, %				
					N	S	halo- gen	C	H	N	S	halo- gen	
(I)	p-Nitrotolyl- $\beta$ -cyanoethylsulfide	72-73°	74	C <sub>9</sub> H <sub>8</sub> O <sub>2</sub> N <sub>2</sub> S	13.36	14.90	—	—	—	13.46	15.38	—	—
(II)	p-Nitrotolyl- $\beta$ - cyanochloroethylsulfide	75-79	79	C <sub>9</sub> H <sub>7</sub> O <sub>2</sub> N <sub>2</sub> SCl	11.38	12.94	14.53	44.65	2.89	11.54	13.19	14.63	44.53
(III)	p-Nitrotolyl- $\beta$ - cyanoethylsulfide	85-86	75	C <sub>9</sub> H <sub>7</sub> O <sub>2</sub> N <sub>2</sub> SBr	9.63	11.26	27.60	—	—	9.75	11.15	27.87	—
(IV)	o-Nitrotolyl- $\beta$ -cyanoethylsulfide	78	73	C <sub>9</sub> H <sub>8</sub> O <sub>2</sub> N <sub>2</sub> S	13.47	14.98	—	—	—	13.46	15.38	—	—

Note: (I) Ar = p-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, X = H; (II) Ar = p-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, X = Cl; (III) Ar = p-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, X = Br; (IV) Ar = o-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, X = H.

TABLE 2  
Aryl- $\beta$ -Carboxyethylsulfides, ArSCH<sub>2</sub>CHXCOOH

Compound No.	Name	M. p.	Yield, %	Empirical formula	Found, %				Calculated, %			
					N	S	N	S	N	S	N	S
(V)	p-Nitrotolyl- $\beta$ -carboxyethylsulfide	129-130°	84	C <sub>9</sub> H <sub>8</sub> O <sub>4</sub> NS	6.30	14.14	6.16	14.09	—	—	—	—
(VI)	p-Nitrotolyl- $\beta$ -chlorocarboxyethylsulfide	126-127	80	C <sub>8</sub> H <sub>8</sub> O <sub>4</sub> NSCl	5.50	—	5.35	—	—	—	—	—
(VII)	o-Nitrotolyl- $\beta$ -carboxyethylsulfide	138-139	80	C <sub>9</sub> H <sub>8</sub> O <sub>4</sub> NS	6.30	13.94	6.16	14.09	—	—	—	—

Note: (V) Ar = p-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, X = H; (VI) Ar = p-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, X = Cl; (VII) Ar = o-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, X = H.

TABLE 3  
Aryl- $\beta$ -cyanoethylsulfones,  $\text{ArSO}_2\text{CH}_2\text{CHXCN}$

Com- pound No.	Name	M. p.	Yield, %	Found, %				Calculated, %			
				N	S	halo- gen	C	H	N	S	halo- gen
(VIII)	p-Nitrotolyl- $\beta$ - cyanoethylsulfone	134–135°	85	11.57	13.13	—	45.00	3.51	11.66	13.33	—
(IX)	p-Nitrotolyl- $\beta$ - chlorocycanoethylsulfone	123–124	84	9.88	11.89	12.50	—	—	10.20	11.65	12.43
(X)	p-Nitrotolyl- $\beta$ - bromocycanoethylsulfone	148–149	80	8.50	10.40	25.10	—	—	8.77	10.03	25.07
(XI)	o-Nitrotolyl- $\beta$ - cyanoethylsulfone	102–103	82	11.57	13.50	—	45.30	3.43	11.66	13.33	—

Note: (VIII) Ar = p- $\text{NO}_2\text{C}_6\text{H}_4$ , X = H; (IX) Ar = p- $\text{NO}_2\text{C}_6\text{H}_4$ , X = Cl; (X) Ar = p- $\text{NO}_2\text{C}_6\text{H}_4$ , X = Br; (XI) Ar = o- $\text{NO}_2\text{C}_6\text{H}_4$ , X = H

TABLE 4  
Aryl- $\beta$ -carboxyethylsulfones,  $\text{ArSO}_2\text{CH}_2\text{CHXCOOH}$

Com- pound No.	Name	M. p.	Yield, %	Empirical formula	Found, %			Calculated, %		
					N	S	halo- gen	N	S	halo- gen
(XII)	p-Nitrotolyl- $\beta$ -carboxyethylsulfone	170—171°	84	C <sub>9</sub> H <sub>9</sub> O <sub>6</sub> NS	5.16	12.53	—	5.40	12.36	—
(XIII)	p-Nitrotolyl- $\beta$ -chlorocarboxyethylsulfone	146—147	80	C <sub>9</sub> H <sub>8</sub> O <sub>6</sub> NSCl	4.77	11.00	11.75	4.79	10.90	12.09
(XIV)	o-Nitrotolyl- $\beta$ -carboxyethylsulfone	139—140	80	C <sub>9</sub> H <sub>9</sub> O <sub>6</sub> NS	5.30	12.56	—	5.40	12.36	—

Note: (XII) Ar = p- $\text{NO}_2\text{C}_6\text{H}_4$ , X = H; (XIII) Ar = p- $\text{NO}_2\text{C}_6\text{H}_4$ , X = Cl; (XIV) Ar = o- $\text{NO}_2\text{C}_6\text{H}_4$ , X = H.

oxidant, and hydrogen peroxide calculated at 3 moles per 1 mole of starting sulfide. The reaction mixture was stirred at 60-70° for 3-4 hours. The solvent was distilled off in a vacuum and the remaining crystals were washed with water and alcohol. After crystallization from alcohol the sulfones were colorless crystals, soluble by heating in alcohol, benzene and acetone, and insoluble in water and ether (Table 3).

Aryl-β-carboxyethylsulfones (XII-XIV). Saponification of the sulfones (VIII, IX, XI) was carried out with 37% hydrochloric acid. Two g of sulfone and 20 ml of hydrochloric acid were stirred at 95-97° for 4-5 hours. After one hour from beginning of the heating we added 10 ml of water to the reaction mixture. At the end of the reaction the colorless crystals which precipitated were washed with cold water and then with alcohol. After crystallization from aqueous alcohol the sulfones were colorless crystals, easily soluble in dioxane, carbon tetrachloride, and not soluble in benzene (Table 4).

p-Nitrophenyl-β-carbomethoxyethylsulfide (XV). To a mixture of 2 g of freshly prepared p-nitrophenylmercaptan [8] with m.p. 76°, 5 ml of anhydrous methanol and 2 drops of triethylamine was added 1.5 ml of methylacrylate stabilized with hydroquinone. The reaction mixture was heated in a nitrogen atmosphere to 50° for 30 minutes and kept for 12 hours at room temperature. The crystals which precipitated were filtered off and washed with alcohol and ether. Yield 2.5 g (80.4%). After crystallization from ligroin the resulting crystals with a yellow tint melted at 58-59°. They were easily soluble in dioxane, chloroform and dichloroethane, and insoluble in water.

Found %: N 6.09; S 13.18; C 49.69; H 4.70.  $C_{10}H_{11}O_4NS$ . Calculated %: N 5.81; S 13.27; C 49.79; H 4.56.

Condensation of sulfide (II) with semicarbazide, thiosemicarbazide and potassium thiocyanate. To a solution of 1 g of sulfide (II) in 40 ml of 96% alcohol we added a water solution of semicarbazide or thiosemicarbazide calculated at 2 mole per 1 mole of starting sulfide (II). The reaction was carried out with continuous stirring at 80° for 15-25 hours. In all cases after removal of the solvent the starting product precipitated. In an analogous way the reaction was carried out with sulfide (III) and potassium thiocyanate. As the solvent we used 20% methyl alcohol, ethyl alcohol, acetone. In all cases the starting sulfides (II, III) were obtained.

p-Nitrophenyl-β-cyanovinylsulfone (XVI). The reaction of sulfone (XI) with semicarbazide and with thiosemicarbazide was carried out in an atmosphere of nitrogen.

1. To a solution of 0.5 g (0.0015 mole) of sulfone (X) heated to 60° in 10 ml of 96% alcohol was added a solution of 0.3 g (0.003 mole) of semicarbazide in 5 ml of alcohol. After four-hour heating on a water bath to 60-70°, colorless crystals precipitated, after which the reaction mass was kept for 12 hours. Then the precipitate was filtered off, washed with water, with alcohol, and dried in a vacuum desiccator. Yield 0.2 g. The resulting substance was colorless and crystalline, melting at 147-148°, easily decolorizing a solution of potassium permanganate.

2. The reaction of sulfone (X) with thiosemicarbazide was carried out in an analogous way. We isolated a substance with m. p. 147-148° which gave no melting point depression with the substance obtained from the preceding experiment. The identity of these substances was also confirmed by analysis.

Found %: N 11.87; S 13.20.  $C_9H_8O_4N_2S$ . Calculated %: N 11.76; S 13.44.

#### SUMMARY

1. We have studied the reaction of addition of o- and p-nitrophenylmercaptans to acrylonitrile, α-chloro- and α-bromoacrylonitrile in the presence of organic bases.
2. We have established that chlorine in p-nitrophenyl-β-cyanochloroethylsulfide under the experimental conditions is not sufficiently mobile and does not react by nucleophilic substitution with semicarbazide, thiosemicarbazide and potassium thiocyanate.
3. We have shown that p-nitrophenyl-β-cyanobromoethylsulfone with semicarbazide and thiosemicarbazide in alcohol-water solution splits out hydrogen bromide and forms an unsaturated sulfone.

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## METHYLOLHALOMALONATES

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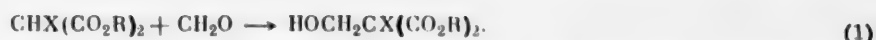
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Methylolhalomalonates,  $\text{HOCHX}(\text{CO}_2\text{R})_2$ , are interesting as polyfunctional compounds in some cases of polycondensation.

We have planned to synthesize and compare the properties of bromo- and fluoromethylolmalonates. For this purpose we studied the reaction of formaldehyde with diethyl halomalonates which, as we would expect, should go according to the scheme:



Actually, bromomalonate ester in the presence of organic bases as catalysts reacts easily with formaldehyde, giving good yields of nondistilling methylol derivatives which were identified in the form of individual acetomethylol- and chloromethylbromomalonate esters, obtained by treatment of the methylol derivatives with acetic anhydride and thionyl chloride, respectively.

However, obtaining methylolfluoromalonate ester met with an unexpected obstacle. In the synthesis of fluoromalonate ester by exchange reaction of potassium fluoride with bromomalonate ester [1], we noted that this exchange based on bromine occurred up to 80%, but the yield of fluorine-containing compound totaled only 20%. Along with the latter there was formed a considerable amount of tarry products from which, with a 25% yield (see equation 2), we isolated the ethyl ester of ethylenetetra-carboxylic acid.

Since bromomalonate ester under the conditions of the reaction (190°, 12 hours) does not undergo exchange with KF itself into ethylenetetra-carboxylic ester, as special experiments showed, we must assume that formation of the latter goes through fluoromalonate ester, which is due to the presence of potassium fluoride.



This reaction is definitely analogous to the reaction of pyrolytic splitting of difluorochloromethane into tetrafluoroethylene.

The resulting fluoroorganic product of this reaction was isolated in the form of a colorless oil which was evidently the monofluoromalonate ester. However, a study of the condensation of this "fluoromalonate" ester with formaldehyde showed that this oil was a mixture of fluoromalonate ester with difluoromalonate and unsubstituted malonate esters, and the latter two were present in the mixture in equimolecular amounts. The content of difluoromalonate ester in the mixture was 40% by weight.

When the reaction of condensation of this mixture of malonates with formaldehyde was carried out, diethyl-difluoromalonate remained as an insoluble oil which after separation and purification corresponded in all its properties (constants and analysis of ester and amide) to diethyldifluoromalonate. Part of the "fluoromalonate" ester which formed a methylol derivative after its isolation gave dimethylolmalonate and methylolfluoromalonate ethyl esters. This follows from a study of the chloromethylmalonates obtained by treatment of the mixture of methylol derivatives with thionyl chloride, as a result of whose fractionation we separated diethyl bischloromethylmalonate  $(\text{ClCH}_2)_2\text{C}(\text{CO}_2\text{C}_2\text{H}_5)_2$  and diethyl chloromethylfluoromalonate  $\text{ClCH}_2\text{FC}(\text{CO}_2\text{C}_2\text{H}_5)_2$ .

The boiling points of diethyl malonate, diethyl fluoromalonate and diethyl difluoromalonate were so close that their separation by ordinary vacuum fractionation was difficult. This was confirmed by the recent work of

Bergmann and co-workers, who synthesized diethyl monofluoromalonate [2]. In this work they described the reaction of bromomalononic ester with potassium fluoride in acetamide; the sole product of this reaction was diethyl difluoromalonate and the formation of the monofluoro ester was not found by these authors, in distinction to our work. Our results for the exchange reaction of monobromomalononic ester with KF, in which from the monohalogen derivative, besides the monofluoromalononic ester, we found mostly an equimolecular mixture of malonate and difluoromalononic ester, that is, the dihalogen derivative, seem to be of interest as a case of unusual disproportionation of a haloorganic compound, the mechanism of which deserves investigation.



## EXPERIMENTAL

1. Condensation of bromomalononic ester with formaldehyde: methylol-, acetoxymethyl- and chloromethylbromomalononic diethyl ester. To 50 g of bromomalononic ester at room temperature with energetic stirring was added 5 ml of pyridine, 20 drops of piperidine and 36.5 g of a 36% formalin solution. The mixture was stirred for five hours and left over night. The layers were separated, the lower layer was washed with 10%  $\text{H}_2\text{SO}_4$  (25 ml) and water (25 ml). We added 50 ml of ether and the solution was dried over calcium chloride.

The ether was distilled off and the residue was kept in a vacuum to remove traces of ether and formaldehyde solution. The weight of crude methylolbromomalononic diethyl ester was 48.5 g. This was a thick, heavy liquid with  $d_{20}^{20}$  1.4667 which decomposed on distillation. The acetate of methylolbromomalononic diethyl ester was obtained by heating the crude methylolbromomalononic diethyl ester (23.5 g) for two hours with 40 g of acetic anhydride in the presence of 2 drops of sulfuric acid. The reaction mixture was poured into 300 ml of water, the lower layer was separated, dried over calcium chloride, and distilled. We obtained 12.5 g of product.

B.p. 137–138° (5 mm),  $n_D^{20}$  1.4530,  $d_{20}^{20}$  1.3576,  $\text{MR}_D$  62.19. Calculated 61.11. Found %: C 39.02; H 5.49; Br 26.35.  $\text{C}_{10}\text{H}_{15}\text{O}_6\text{Br}$ . Calculated %: C 38.58; H 4.82; Br 25.73.

To obtain chloromethylbromodiethylmalonate, 21 g of the condensation product was added at room temperature to 30 g of thionyl chloride, and then the mixture was heated on a water bath for 30 minutes. The excess thionyl chloride was distilled off and the residue was distilled in a vacuum. We collected 11.3 g of product.

B.p. 126–129° (10 mm),  $d_{20}^{20}$  1.4573,  $n_D^{20}$  1.4680,  $\text{MR}_D$  54.95. Found %: C 33.36; H 3.93; Cl+Br 36.60.  $\text{C}_8\text{H}_{12}\text{O}_4\text{ClBr}$ . Calculated %: C 33.32; H 4.17; Cl+Br 40.50.

2. Fluorination of the bromomalononic ester. A mixture of 140 g of pure bromomalononic ester and 42 g of potassium fluoride, ignited and sifted through a fine sieve, was heated in a reactor with intensive stirring for 12 hours at 190°. The reactor was fitted with a condenser, and during the reaction a small amount of liquid (8–10 g) distilled off. At the end of heating, the reaction mixture was filtered from the precipitate and the latter was carefully washed with ether. The filtrate along with the wash liquid was distilled. We collected 24.2 g of product.

B. p. 76–78.5° (10 mm),  $n_D^{20}$  1.3983,  $d_{20}^{20}$  1.1475,  $\text{MR}_D$  37.52. Calculated 37.73. Found %: C 46.40; H 6.06; F 10.1.  $\text{C}_7\text{H}_{11}\text{O}_4\text{F}$ . Calculated %: C 47.22; H 6.18; F 10.69.

The residue in the distilling flask (42 g) was treated with alcohol. A white crystalline substance separated (14 g). M.p. 54°. After distillation at 198° (8 mm) and recrystallization from a mixture of benzene and ligroin (1:1) m. p. 57°. According to the literature [3], ethylene tetracarboxylic ester has b.p. 197° (8 mm) and m.p. 57–58°.

3. Condensation of the product of fluorination of bromomalononic ester with formaldehyde; preparation of difluoro- and chloromethylfluoromalononic diethyl esters. Twenty-five g of fluorination product (fraction 76–78.5° at 10 mm), 50 g of 36% formalin and 1 g of triethylamine were stirred at room temperature for five hours. On the next day the reaction mixture, a liquid with two layers, was separated. The lower layer (11.1 g) was distilled. We collected 6.3 g of difluoromalononic diethyl ester.

B.p. 73–75° (10 mm),  $n_D^{20}$  1.3830,  $d_{20}^{20}$  1.2135,  $\text{MR}_D$  37.73. Calculated 37.63. Found %: F 18.60.  $\text{C}_7\text{H}_{10}\text{O}_4\text{F}_2$ . Calculated %: F 19.36.

In the usual way we obtained from the ester its amide, m. p. 205–207°, identical with the amide of difluoromalononic acid. According to [4], m.p. 206.5–206.7°.



Found %: F 26.20; N 19.70.  $C_3H_4O_2N_2F_2$ . Calculated %: F 27.6; N 20.3.

For extraction of the condensation product, the upper water layer was treated with ether. The ether extract was dried over sodium sulfate and the ether was distilled off. The residue (16.6 g) was kept in a vacuum ( $n_D^{20}$  1.4380,  $d_{20}^{20}$  1.2103; %F 3.94), after which it was treated with thionyl chloride [5]; we collected 4.5 g of a fraction with b.p. 70-140° (6 mm), %Cl 23.8, %F 2.1. By repeated distillations we obtained 0.5 g of diethyl chloromethylfluoromalonate (a) and 2.2 g of dichloromethyldiethylmalonate (b).

a) B.p. 95-100° (12 mm),  $n_D^{20}$  1.4200.

Found %: F 8.9; Cl 16.4.  $C_8H_{12}O_4FCl$ . Calculated %: F 8.4; Cl 13.8.

b) B.p. 120° (12 mm),  $n_D^{20}$  1.4400.

Found %: Cl 26.60.  $C_9H_{14}O_4Cl_2$ . Calculated %: Cl 27.73.

#### SUMMARY

1. Diethyl bromo- and fluoromalonates condense with formaldehyde with formation of methylol compounds which have been identified by conversion to the corresponding acetyl and chloromethyl derivatives.
2. In the exchange reaction of bromomalononic diethyl ester with potassium fluoride, along with the normally formed fluoromalononic ester, there occurs chiefly an unusual disproportionation of the monohalogen derivative leading to formation of difluoromalononic diethyl ester. The chief reaction in this is the formation of ethylenetetra-carboxylic ester.

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## THE PROBLEM OF TRANS - ENOLIZATION

### I. THE EFFECT OF SOLVENTS ON ENOLIZATION OF "TRANS-FIXED"

#### KETOENOLS

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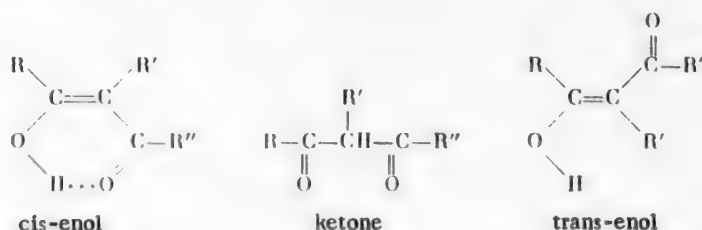
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At the present time it can be considered established [1] that in the usual case in solutions of  $\beta$ -dicarbonyl compounds with open chains there is an equilibrium to a definite extent of three forms: the ketone and the cis- and trans-enols.



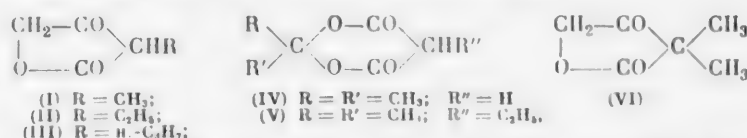
Equilibrium of these three forms is determined by their ionization constants in the given solvent, which, in turn, depends on the "intrinsic acidity" of the form and its solvation [2].

Since the publications of Sedgewick [3,4], it has been considered that the enol form of acetoacetic ester and other similar ketoenols has the cis-configuration with intramolecular hydrogen bonds. In distinction to the ketone form it is characterized by a comparatively low boiling point and better solubility in nonpolar (hydrophobic) solvents than in polar (hydrophilic) ones. Hence, in full agreement with the van't Hoff-Dimroth rule [5], nonpolar solvents shift the tautomeric equilibrium toward the enol (cis) form, and polar ones, toward the ketone form. These relations are expressed by the well known Meyer rule [6],  $K_T = EL$ , where  $K_T$  is the tautomeric equilibrium constant of the ketoenol in solution, E the enolizability of the ketoenol, independent of the solvent, L the enolizing ability of the solvent, equal to the equilibrium constant of the standard substance, acetoacetic ester ( $E=1$ ). The value of L changes from  $4 \cdot 10^{-3}$  for water to 1 for hexane. The graphic relation of  $K_T$  to L for ketoenols obeys the Meyer rule, and is expressed by a straight line passing through the origin.

However, the picture is complicated when along with the cis-enol form a considerable amount of trans-enol form appears. The first example of such a type was formylphenylacetic ester [7]. A number of examples of the existence of the enol form in the trans-configuration were shown by Henecka [8] based on the inability of these enols to give a color reaction with ferric chloride. Two of these substances varied from the Meyer rule.

The problem of trans-enolization was first discussed in detail by Arndt, Loewe and Ginkōk [9]. These authors turned their attention to the contradiction in the fact that hydrophilic solvents shifted the equilibrium not toward the more polar trans-enol form, which contains an open hydroxyl group, but toward the ketone form, and these authors showed the formation of a ketone form of hydrate or hemiacetal which was highly polar and imitated the reactions of the ketone form. However, the hypothesis of Arndt et al. met with objections [2,10]. Neither was it confirmed by a study of the effect of pressure on the position of the ketoenol equilibrium [11]. Eistert and Reiss [12] considered a cyclic ketoenol which contained both carbonyl groups in one ring and so would not permit the formation of a cis-enol form, but the formation of a "trans-fixed" enol. Here, in the opinion of these authors, the effect

of the solvent on the position of the keto-trans-enol equilibrium should be the reverse of the Meyer rule, that is, hydrophilic solvents should shift the equilibrium to the enol form, and hydrophobic ones to the keto. Bromometric analysis of the solutions of such ketoenols in different solvents gave very inexact and difficultly reproducible figures, but in general confirmed the hypothesis. Thus, in solutions of  $\alpha$ -methyltetronic acid (I) in ether, methanol, and water the enol was present, respectively, 69, 97, and 100%, and in cyclic isopropylidene malonate (IV) ("Meldrum acid") in benzene, methanol and water, respectively, 37, 95, and 128%.



In a number of other cases this hypothesis was confirmed spectrally. However, in this work spectral data were given by other authors [13, 14] which agreed poorly with this hypothesis, in studies with  $\alpha$ -ethyltetronic acid (II). The assumption of the German authors rather corresponded to the results of Russell [15], who found by the use of ultraviolet spectra that in solutions of  $\beta$ -cyanoketones whose enol forms could not give internal complex formation for steric reasons and therefore contained open hydroxyl groups [16, 17], the content of the enol form in hydroxyl-containing solvents was higher than in hydrophobic ones. However, careful consideration of the data of Russell gave a more complex picture: in the series of hydroxyl-containing solvents water-methanol-ethanol-pentanol, the content of enol increased with decreasing hydrophilic nature of the solvent; it passed through a maximum with pentanol, then fell in ether (but remained higher in ether than in water), and then fell sharply in a mixture of ether and hexane and was lowest of all in hexane. Such an effect of the hydrophilic nature of the solvent obeyed neither the Meyer rule nor the hypothesis of Eistert and Reiss.

In the work mentioned above one of us [2] considered keto-cis-trans-enol equilibria as acid-base equilibrium of three acids which had a common anion. This equilibrium followed the usual rules of acid-base equilibrium expressed in the theory of Brønsted-Izmailov [18-22]. In solutions of ketoenols with open chains, cis- and trans-forms are present in the usual case, but the trans-enol form usually has considerably greater "intrinsic acidity"; therefore, its relative content is always small and the ketoenol equilibrium obeys the Meyer rule. However, in polar solvents which solvate the trans-form better, when the total content of enol is decreased (because of cis-enol) the relative content of trans-enol form in the enol fraction of the ketoenol rises. This removes the problem of Arndt.

In the following communication on this theme [23], we showed that the effect of solvents on keto-cis-trans-enol equilibrium could be quantitatively calculated from an expanded formula analogous to the Meyer formula, but considering the trans-enolization:

$$K_T = EL + E'L' \quad (1)$$

where E is enolizability of the ketoenol on the side of cis-enol, i.e., the constant E of Meyer; E' the same on the side of trans-enol; L the enolizing power of the solvent on the side of the cis-enol (L of Meyer); and L' the same on the side of the trans-enol. This relation is expressed, like the Meyer formula itself [24], as a direct consequence of the Brønsted-Izmailov equation, and is not based on any other assumption besides the idea of acid-base equilibrium for solutions of ketones and the cis- and trans-enol forms.\* Application of this formula requires the use of a standard substance, one for cis-enolization (E' = 0, E = 1) and another for trans-enolization (E = 0, E' = 1). As the standard substance for cis-enolization it was possible to keep acetoacetic ester. The case was more complex with the standard for trans-enolization. We have studied the effect of solvents on enolization of the  $\alpha$ -substituted acetoacetic esters investigated by Henecka [8] by the bromometric [23] and spectral [25] methods. It was shown that of these the ones which were capable only of trans-enolization were characterized in all solvents by practically constant tautomeric equilibrium constants. The greater the ability for cis-enolization, the more strongly did these constants depend on the solvent. For  $\alpha$ -sec-butylacetoacetic ester, for example, for which the formation of the cis-enol form is sterically very difficult, the content of enol form is practically constant in benzene, ethanol, methanol and 67% methanol. This shows that for trans-enolization of ketoenols of this type the constant L' hardly changes, and formula (1) is changed to the simpler form (2):

$$K_T = EL + E_L \quad (2)$$

\* In formula (1) the parameters L and L' have a constant value for substances of one chemical type, since this formula comes from the well known relation  $\text{pK}_{A_1} = \text{pK}_{A_2} + C$ , in which the value of C is a constant only for acids of the same chemical type.

where  $E_1$  is some constant value which characterizes the trans-enolizability of  $\alpha$ -substituted acetoacetic esters in all solvents. It seems that this conclusion finds confirmation as a result of bromometric determination of the content of the enol form in solutions of some cyclic "trans-fixed" ketoenols carried out by the reverse method of Meyer [23].\* Moreover, use of formula (2) permits calculation of the content of cis- and trans-forms in solutions of some  $\alpha$ -substituted acetoacetic esters in a number of solutions.

In a recently published work of Eistert and Geiss [26] they studied the enolization of some "trans-fixed" ketoenols by the spectral method. They showed that both our results [23] and those of Eistert and Reiss [12] on the bromometric determination of the content of the enol form in solutions of strongly acid ketoenols did not agree with the results of spectral investigation. Thus, for example, they showed that isopropylidene malonate (IV), which according to the bromometric determination results [12] enolized in different solutions 37-128%, or isopropylideneethyl malonate (V), which by our bromometric determination contained about 70% enol, were not enolized at all. Since the spectral results in this and analogous cases are more reliable, we must recognize the nonapplicability of the bromometric method to this class of compounds. We will not linger on the source of error of the bromometric method on using it in strongly acid cyclic  $\beta$ -dicarbonyl compounds of this type. We note only that, besides the brominated anion, perhaps, an important part is played by the ketone form which is rapidly brominated directly.\*\*

In connection with these facts, two basic questions again arise.

1) What is the actual effect of solvents on the enolization of "trans-fixed" cyclic ketoenols of different types and how much can we apply to them the hypothesis of the German authors on the application of the Meyer rule.

2) What is the effect of solvents on trans-enolization of ketoenols with open chains, how satisfactory is formula (2) and what substance can be used as the standard for trans-enolization of  $\beta$ -ketoesters.

Below we give the results of further experimental investigation carried out to obtain an answer to the first question. The second question will be considered in communication II of the present investigation.

$\alpha$ -Alkyltetronic acids. In the opinion of Eistert and Geiss [26] in solutions of  $\alpha$ -ethyltetronic acid (II), analogously to solutions of the isopropylidenealkyl malonate type (IV) and (V) there should be an equilibrium of only the keto form with the corresponding enolate anion. The close agreement which we observed earlier of the absorption curves (ultraviolet spectra) of ethyltetronic acid in water, methanol and ethanol was explained by them as to a considerable degree a chance agreement of the concentration of enolate anion in the solutions studied. Also, the data of Dunkanson [13] and of Herbert and Hirst [14] for  $\alpha$ -ethyltetronic acid, which agreed closely with ours and showed an approximate constancy of enolization of  $\alpha$ -ethyltetronic acid in such different solvents as aqueous sulfuric acid and ethylene chloride, was neglected by the German authors, although they had cited it in previous publications.

We found that infrared spectra of crystalline  $\alpha$ -ethyl- and  $\alpha$ -propyltetronic acids (Fig. 1 a and b) actually differed in the region 1800 and 2600-3000  $\text{cm}^{-1}$  from the infrared spectrum of the lactone of  $\gamma$ -hydroxy- $\alpha, \alpha$ -dimethylacetoacetic acid (VI), a compound analogous in structure, but with a fixed ketone form (Fig. 1c). In the spectrum of this lactone the bands 1745 and 1798  $\text{cm}^{-1}$  are certainly related to valence oscillation of the ketonic and carboxyl carbonyls.\*\*\* In the region 2600-3300  $\text{cm}^{-1}$  in the spectra of these compounds there is only the frequency characteristic of C-H.

In the infrared spectra of crystalline ethyl- and propyltetronic acids (II and III), we found a widely diffused band in the region 3050-2950  $\text{cm}^{-1}$  and an intense band 2710  $\text{cm}^{-1}$ . The character and position of these bands gives a basis for relating them to valence oscillation of the hydroxyl group involved in an intermolecular hydrogen bond. Hence, the  $\alpha$ -alkyltetronic acids studied in the crystalline state have an enol structure. This conclusion agrees well with the findings of the absorption bands of these substances in the region of valence oscillation of the double bonds 1650 and 1715  $\text{cm}^{-1}$ . The first band can evidently be connected with oscillation of the C = C bond of the enol form,

\* In the work mentioned [23], the use of the method of direct bromometric titration of these substances was erroneously shown.

\*\* In direct titration of a benzene solution of (V) and a solution of (III) in aqueous methanol by a solution of bromine in methanol or ethanol, the amount of bromine used corresponds to 100% enol content.

\*\*\* The higher values of these frequencies compared to the frequency of analogous oscillation of noncyclic  $\beta$ -dicarbonyl compounds is evidently explained by a specific five-membered ring. It is known [27] that in cyclic compounds which contain the group C=O, the frequency of valence oscillation of the carbonyl group rises with growth in the strain of the ring.

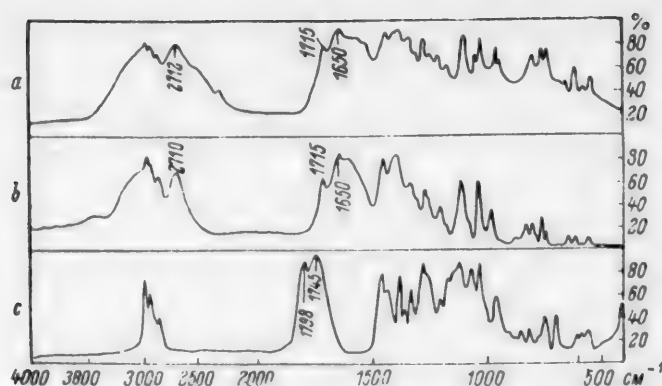


Fig. 1. Infrared spectra of alkyltetronic acids, a)  $\alpha$ -ethyltetronic; b)  $\alpha$ -propyltetronic; c) lactone of  $\gamma$ -hydroxy- $\alpha,\alpha$ -dimethylacetoacetic.

the second with oscillation of the C=O bond in it.\* The lowered frequency of C=O compared to the oscillation frequency of the carbalkoxyl of the lactone mentioned (Fig. 1 c)  $1798\text{ cm}^{-1}$  is explained by intermolecular hydrogen bonds and conjugation.\*\*

The ultraviolet spectrum of  $\alpha$ -propyltetronic acid was studied in water (at pH 2.50, 2.90, 3.35, 3.75, 11.20), methanol, ethanol, ether, dioxane and dichloroethane (Figs. 2 and 3); the spectrum of the lactone (VI) in methanol (Fig. 4). As the absorption curves show, the electronic spectra of  $\alpha$ -propyltetronic acid and the model lactone (VI), which has a ketone structure, differ greatly from each other in position and intensity of absorption bands. Hence, in solutions of  $\alpha$ -propyltetronic acid the tautomeric equilibrium is not shifted toward the ketone form. In water solution at high pH value (11.20) there is a very intense maximum at  $258\text{ m}\mu$ , which certainly characterizes absorption of the anion of  $\alpha$ -propyltetronic acid [13, 14]. At lower pH the intensity of this maximum falls, and in strongly

acid media there appears a rather intense absorption maximum at  $233\text{ m}\mu$ , which can correspond only to the undissociated molecule of  $\alpha$ -propyltetronic acid. From the character of the absorption it does not correspond to the ketone form, and hence agrees with the enol form.\*\*\* Thus, the observed change in ultraviolet spectrum with change in pH characterizes the equilibrium of ionic dissociation of the enol form of  $\alpha$ -propyltetronic acid. The ultraviolet absorption curves in acidified water, methanol and ethanol, as we reported previously [23], practically agree (Fig. 2), as is shown by the approximate identity of the enolization in these solutions, as also in the dichloroethane solutions. In ether the content of enol form is somewhat higher; it is somewhat higher still in dioxane. Due to the small intensity of absorption in the ultraviolet of the ketone forms of these substances, it is difficult to judge the tautomeric equilibrium constant from these data. It is clear in all cases that depending on the solvent, they change slightly, and the change does not agree with the hypothesis of Eistert and Reiss.

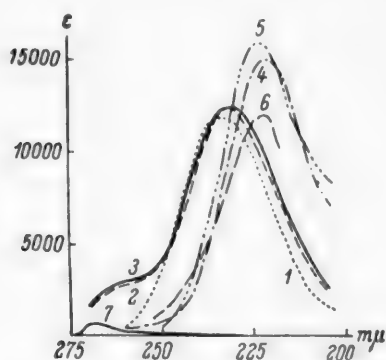


Fig. 2. Ultraviolet spectra of  $\alpha$ -propyltetronic acid at concentration  $5 \cdot 10^{-4}\text{ M}$  in different solvents. 1) Water at pH 2.50; 2) methanol; 3) ethanol; 4) ether; 5) dioxane; 6) dichloroethane; 7) lactone of  $\gamma$ -hydroxy- $\alpha,\alpha$ -dimethylacetoacetic acid in methanol.

\* The frequencies of valence oscillation of the groups C=C and C=O in (II) and (III) can appropriately be compared with the corresponding frequencies of acrylic acid esters. Thus, in the spectra of esters of substituted acrylic acids the frequency of valence oscillation of the C=C group occurs in the region  $1630\text{--}1650\text{ cm}^{-1}$  and of the group C=O in the region  $1715\text{--}1725\text{ cm}^{-1}$  [28].

\*\* Usually conjugation lowers the frequency of C=O by  $20\text{--}40\text{ cm}^{-1}$  [28], and formation of hydrogen bonds by  $50\text{--}60\text{ cm}^{-1}$  [29, 30]. When both factors act together the total lowering of frequency of C=O can reach  $70\text{--}100\text{ cm}^{-1}$ .

\*\*\* The absorption curve is exactly reproduced in the reverse conversion from acid solution to alkaline.

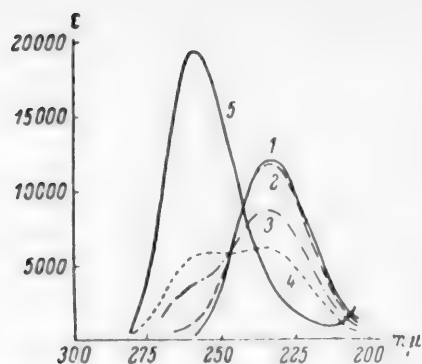


Fig. 3. Ultraviolet spectra of  $\alpha$ -propyltetronic acid in water at different pH values ( $c 5 \cdot 10^{-4}$  M). 1) 2.50; 2) 2.90; 3) 3.35; 4) 3.75; 5) 11.20.

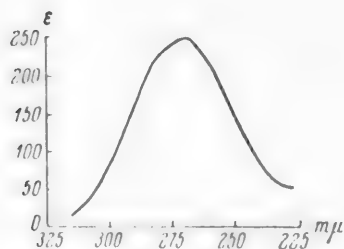


Fig. 4. Ultraviolet spectrum of  $\gamma$ -hydroxy- $\alpha, \alpha$ -dimethylacetoacetic acid in methanol ( $c 5 \cdot 10^{-4}$  M).

There is also agreement with the results of the ultraviolet spectra in the results of the study of infrared spectra of 1% solutions of  $\alpha$ -propyltetronic acid in chloroform, ether, tetrahydrofuran and saturated solution in carbon tetrachloride (Fig. 5). In the spectrum of the chloroform solution (Fig. 5 b), there is an intense band at  $1652$  and  $1730$   $\text{cm}^{-1}$  corresponding closely in position to the enol form. Also in the spectrum are weak bands at  $1768$  and  $1812$   $\text{cm}^{-1}$ , approximately corresponding to the frequency of lactone (VI) and, perhaps, to the ketone form. Therefore, we can assume that on solution of the crystalline enol form in chloroform there results a small amount of ketone form. Analogous bands in the region  $1600$ – $1850$   $\text{cm}^{-1}$  occur in the spectrum of a solution of  $\alpha$ -ethyltetronic acid in chloroform [31]. In the spectrum of a solution of  $\alpha$ -propyltetronic acid in carbon tetrachloride (Fig. 5 d), there are two enol bands  $1660$  and  $1715$   $\text{cm}^{-1}$  and a band  $1761$   $\text{cm}^{-1}$  which can be referred to valence oscillation of  $\text{C}=\text{O}$  of the ketone form, or to valence oscillation of an enol  $\text{C}=\text{O}$  group which does not share in a hydrogen bond. With respect to intensity it is weaker than the corresponding band in chloroform, which can be explained either by smaller content of the ketone form, or by a lesser number of molecules free from hydrogen bonds. The very slightly intense band in the region  $1800$   $\text{cm}^{-1}$  related to the carbonyl group in the ketone form was not found, due to the extremely slight solubility of the substance in carbon tetrachloride. The spectrum of  $\alpha$ -ethyltetronic acid in carbon tetrachloride was studied by Dunkanson [13]. Aside from the three bands mentioned, he was able to find a band at  $1818$   $\text{cm}^{-1}$ . These results agreed with the idea of the appearance of a ketonic form in solutions of  $\alpha$ -alkyltetronic acids in chloroform and carbon tetrachloride.

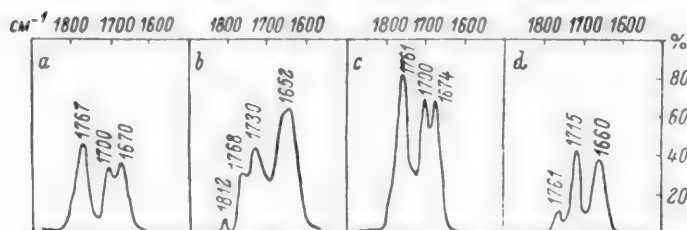


Fig. 5. Infrared spectra of solutions of  $\alpha$ -propyltetronic acid ( $c 1\%$ ). a) In ether; b) in chloroform; c) in tetrahydrofuran; d) in carbon tetrachloride (saturated solution).

In the infrared spectra of  $\alpha$ -propyltetronic acid in ether and tetrahydrofuran (Fig. 5 a and 5 c) there were three clear bands at about  $1670$ ,  $1700$  and  $1760$   $\text{cm}^{-1}$ . Evidently the first belongs to valence oscillation of  $\text{C}=\text{C}$  and the second to  $\text{C}=\text{O}$  enol form (hydrogen bond). The band at  $1760$   $\text{cm}^{-1}$  can belong to  $\text{C}=\text{O}$  in the ketone form, or to enol carbonyl free from hydrogen bonds. The second idea seems more likely to us, since in the first case there should occur along with it a band in the region  $1800$   $\text{cm}^{-1}$ , which is not found. Thus, the results of the infrared spectra confirm the enol form of  $\alpha$ -propyltetronic acid in solutions, and in solutions in chloroform and carbon tetrachloride we can also suspect some small amount of the ketone form.



**Isopropylideneethyl malonate.** In the infrared spectrum of isopropylideneethyl malonate (V) (Fig. 6 a), there is an intense absorption band in the region  $1740-1775\text{ cm}^{-1}$ , which corresponds to the characteristic  $\text{C}=\text{O}$  oscillation of the carbonyl and carboxyl groups in ketone form. The ketone structure of the molecule in the crystalline form

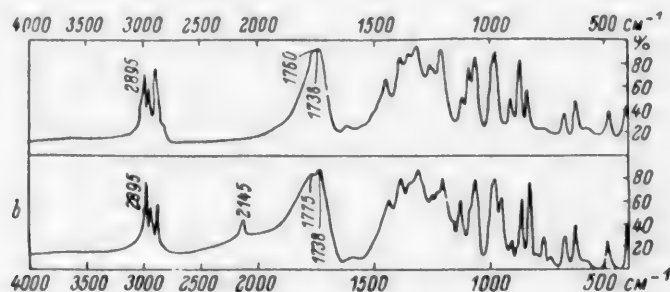


Fig. 6. Infrared spectra of crystalline isopropylideneethyl malonate (a) and monodeuterioisopropylideneethyl malonate (b).

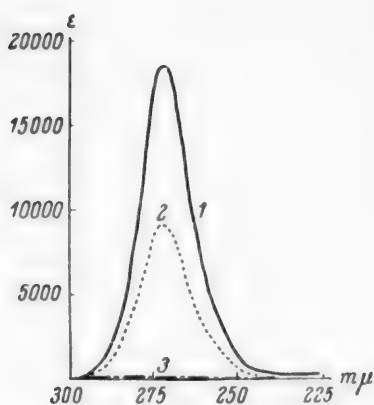


Fig. 7. Ultraviolet spectrum of isopropylideneethyl malonate in methanol. 1) Alkaline; 2) neutral; 3) acid (conditionally!).

solutions; the maximum was restored to the original height on addition of the corresponding amount of alkali. These results, which confirm the results of the German authors, show that in the crystalline state and in solution in non-polar solvents acids of this type exist only in the ketone form. In polar solvents they occur in equilibrium with the enolate anion, the concentration of which is determined by the pH of the medium. These cyclic  $\beta$ -dicarbonyl compounds under no conditions are enolized and thus do not conform either to the Meyer rule or the hypothesis of Eistert and Reiss.

#### EXPERIMENTAL

Isopropylideneethyl malonate was obtained by the method described in [32], m.p.  $107^\circ$ .

Found %: C 56.1; H 7.2, 7.3.  $\text{C}_8\text{H}_{12}\text{O}_4$ . Calculated %: C 55.8; H 7.0.

Deuterioisopropylideneethyl malonate, m. p.  $107^\circ$ .

Found %: C 55.4, 55.2; H 7.01, 7.0.  $\text{C}_8\text{H}_{11}\text{O}_4\text{D}$ . Calculated %: C 55.5; H 7.6.

Ethyltetronic acid with m. p.  $127-128^\circ$  and propyltetronic acid with m. p.  $126^\circ$  were obtained by the method of [33].

Lactone of  $\gamma$ -hydroxy- $\alpha$ ,  $\alpha$ -dimethylacetoacetic acid was synthesized by the method of Konrad [34] from  $\gamma$ -acetoxy- $\alpha$ ,  $\alpha$ -dimethylacetoacetic ester and had b.p.  $72.5^\circ$  (5 mm),  $n_D^{20}$  1.4483,  $d_4^{20}$  1.1496. The literature data give [35]: b. p.  $208-209^\circ$ ,  $d_{15}^{18}$  1.147.

Found %: C 56.2, 56.3; H 6.6, 6.6.  $\text{C}_6\text{H}_8\text{O}_3$ . Calculated %: C 56.2; H 6.3.

is also confirmed by the absence of the absorption band of the hydroxyl group. In the spectrum of solutions of this acid in carbon tetrachloride, there is a sharp band at  $3535\text{ cm}^{-1}$ , which could be related to oscillation of a free hydroxyl group and thus would indicate the appearance of the enol form and of overtones of valence oscillation of the  $\text{C}=\text{O}$  group. In the spectrum of solutions of the monodeutero derivative, the band at  $3535\text{ cm}^{-1}$  remains unchanged, which confirms the latter assumption. Isotopic substitution occurs on the  $\alpha$ -carbon atom of the ketone form, as is indicated by the marked decrease in intensity of the  $2895\text{ cm}^{-1}$  band (in the spectrum of the crystalline compound) as compared to the nondeuterated compound and the appearance of the band  $2145\text{ cm}^{-1}$  (Fig. 6 b).

In the ultraviolet spectra of alkaline, neutral and acid methanol solutions of isopropylideneethyl malonate (Fig. 7), we obtained a picture analogous to that found by Eistert and Reiss [26] in the spectra of its spiro-analog: in alkaline solution they found intense absorption with a maximum at  $272\text{ m}\mu$ ; it was weaker in neutral solutions and vanished in acid

Measurement of the pH of the solutions for spectral study was carried out on an LP-5 lamp potentiometer with an accuracy of 0.05 pH units.

The infrared spectra were obtained on a two-beam IKS-14 spectrometer. Samples for photography of the crystalline compounds were prepared by the method of pressing with potassium bromide. The ultraviolet spectra were obtained on an SFD-1 apparatus. The concentration of the solutions is shown in the text under the figures.

#### SUMMARY

The effect of solvents on enolization of "trans-fixed" ketoenols depends on the nature of the cyclic ketoenol. Enolization of  $\alpha$ -alkyltetronic acids is practically independent of the solvent.

Cyclic acetals of malonic acid in the crystalline state and in solution are practically not enolized. The hypothesis of Eistert and Reiss on the reversal of the Meyer rule for "trans-fixed" ketoenols is evidently valid only for ketoenols of the type of dimedon which these authors studied. The effect of solvents on enolization of ketoenols of the type of alkyltetronic acids or isopropylidenealkyl malonates agrees neither with the Meyer rule nor with the hypothesis of Eistert-Reiss.

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# THE CONDENSATION OF 2,2, 5, 5-TETRAALKYL-3-FURANIDONES WITH ALDEHYDES OF AN AROMATIC CHARACTER

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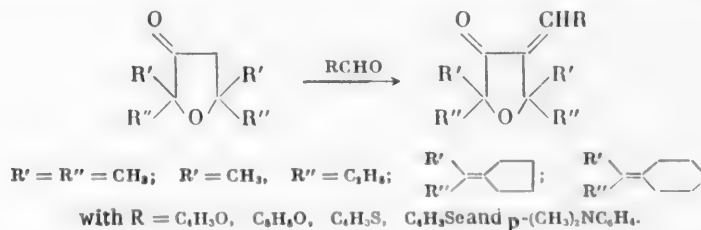
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2,2,5,5-Tetraalkyl-3-furanidones have an active methylene group and easily condense with benzaldehyde in the presence of alkaline agents, potash, sodium hydroxide, or potassium hydroxide, forming 4-benzylidene-2,2,5,5-tetraalkyl-3-furanidones [1-3]. In the case of 2,2,5,5-tetramethyl-3-furanidone it was shown that the reaction occurred smoothly enough not only with benzaldehyde, but with other aromatic aldehydes: cinnamaldehyde, 3, 4-dimethoxybenzaldehyde, o- and m-nitrobenzaldehydes, p-dimethylaminobenzaldehyde, and the yields of 4-arylidene-2,2,5,5-tetramethyl-3-furanidones reached 95% [3].

The reaction of 5,5-dialkyl-3-furanidones with benzaldehyde gave 2-benzylidene-5, 5-dialkyl-3-furanidones, but with a yield of 50% [4]. Condensation of 2,2,5,5-tetramethyl-3-furanidone with aldehydes of the aliphatic series, butyl and isobutyl, gave 4-alkylidene-2,2,5,5-tetramethyl-3-furanidones with yields of only 20 and 27%, respectively. The reaction of 2,2,5,5-tetramethyl-3-furanidone with acetone took place in two directions: with short interaction of the reagents in the presence of sodium methylate, 2,2,5,5-tetramethylfuranlydene-3-acetone was formed [5]; with longer heating, 4-isopropylidene-2,2,5,5-tetramethyl-3-furanidone and products of its further transformations were obtained; methylethyl, methylpropyl, and methyl-tert-butyl ketones reacted in an analogous way [6].

In the present work we have studied the reaction of ketones of the tetrahydrofuran series, 2,2,5,5-tetraalkyl-3-furanidones (2,2,5,5-tetramethyl-, 2,5-dimethyl-2,5-diethyl-, 2,2,5,5-bistetramethylene-, and 2,2,5,5-bispentamethylene-3-furanidones), with such aromatic aldehydes as furfural, 5-methylfurfural, thiophene-2-aldehyde, and selenophene-2-aldehyde, and also p-dimethylaminobenzaldehyde. We showed that the reaction on the methylene group of the 2,2,5,5-tetraalkyl-3-furanidones took place under these conditions with good yields and led to the corresponding  $\alpha$ ,  $\beta$ -unsaturated ketones, whose constants and yields are given in the table.



We should note that in the reaction of 2,5-dimethyl-2,5-diethyl-3-furanidone with furfural, 5-methylfurfural, selenophene-2- and thiophene-2-aldehyde there was formed a noncrystallizing oil, and only in the case of p-dimethylaminobenzaldehyde could we isolate a good yield of 4-(p-dimethylaminobenzylidene)-2,5-dimethyl-2,5-diethyl-3-furanidone.

Selenophene-2-aldehyde, thiophene-2-aldehyde, and p-dimethylaminobenzaldehyde are the most active in this reaction. The  $\alpha$ ,  $\beta$ -unsaturated ketones obtained from them crystallize well and can be used successfully for identification of 2,2,5,5-tetraalkyl-3-furanidones.

## EXPERIMENTAL

To a solution of equimolar amounts of 2,2,5,5-tetraalkyl-3-furanidone and the aldehyde (at 0.005-0.02 M) in 20-30 ml of alcohol we added dropwise 5-10 ml of a 50% solution of potassium hydroxide, and allowed the

Com- pound No.	Name and formula	Yield, %	M. p.	% C		% H	
				found	calculated	found	calculated
(I)	4-Furfural-2,2,5,5-bistetramethylene-3-furanidone, $C_{17}H_{20}O_3$	62	70-71°	74.65, 74.54	74.98	7.41, 7.37	7.40
(II)	4-Furfural-2,2,5,5-bis-pentamethylene-3-furanidone, $C_{19}H_{24}O_3$	95	131-132	75.88, 76.11	75.97	8.20, 8.22	8.05
(III)	4-(5'-Methylfurfural)-2,2,5,5-tetramethyl-3-furanidone, $C_{14}H_{18}O_3$	Quantitative	76-77	72.11, 72.15	71.77	7.69, 7.89	7.74
(IV)	4-(5'-Methylfurfural)-2,2,5,5-bistetramethylene-3-furanidone, $C_{18}H_{22}O_3$	70	67-68	75.23, 75.34	75.49	7.78, 7.80	7.75
(V)	4-(5'-Methylfurfural)-2,2,5,5-bis-pentamethylene-3-furanidone, $C_{20}H_{26}O_3$	92	109-110	76.28, 76.44	76.40	8.32, 8.51	8.34
(VI)	4-Thenal-2'-2,2,5,5-tetramethyl-3-furanidone, $C_{13}H_{16}O_2S$	Quantitative	112-113	66.26, 66.33	66.06	6.98, 6.92	6.84
(VII)	4-(Thenal-2'-2,2,5,5-bistetramethylene-3-furanidone, $C_{17}H_{20}O_2S$	96	92-93	70.58, 70.32	70.81	6.92, 6.92	6.99
(VIII)	4-(Thenal-2'-2,2,5,5-bis-pentamethylene-3-furanidone, $C_{19}H_{24}O_2S$	94	100-101	72.03, 71.84	72.10	7.83, 7.73	7.64
(IX)	4-(Selenenal-2'-2,2,5,5-tetramethyl-3-furanidone, $C_{13}H_{16}O_2Se$	Quantitative	126-127	55.25, 55.27	55.13	5.81, 5.87	5.69
(X)	4-(Selenenal-2'-2,2,5,5-bistetramethylene-3-furanidone, $C_{17}H_{20}O_2Se$	Quantitative	107-108	60.72, 60.64	60.89	6.15, 6.01	6.01
(XI)	4-(Selenenal-2'-2,2,5,5-bis-pentamethylene-3-furanidone, $C_{19}H_{24}O_2Se$	70	123-125	62.45, 62.99	62.80	6.75, 6.66	6.66
(XII)	4-(p-Dimethylaminobenzylidene)-2,5-dimethyl-2,5-diethyl-3-furanidone, $C_{19}H_{27}O_2N$	Quantitative	127-128	75.79, 75.96	75.71	9.27, 9.21	9.03
(XIII)	4-(p-Dimethylaminobenzylidene)-2,2,5,5-bis-tetramethylene-3-furanidone, $C_{21}H_{27}O_2N$	92	163-164	77.11, 77.29	77.48	8.39, 8.25	8.36
(XIV)	4-(p-Dimethylaminobenzylidene)-2,2,5,5-bis-pentamethylene-3-furanidone, $C_{23}H_{31}O_2N$	90	139-140	—	—	—	—

• Found %: N 4.63, 4.83. Calculated %: N 4.65.

•• Found %: N 4.06, 4.23. Calculated %: N 3.96.

reaction mixture to stand 12-18 hours; the resulting compound was crystallized from alcohol. Compounds (I-IV and XI) were separated in the crystalline state only after acidification of the reaction mixture with dilute acetic acid.

The constants and yields of the resulting  $\alpha$ ,  $\beta$ -unsaturated ketones of the 2,2,5,5-tetraalkyl-3-furanidone series are given in the table.

#### SUMMARY

2,2,5,5-tetraalkyl-3-furanidones react easily with aromatic aldehydes and heterocyclic aldehydes with an aromatic character; the reaction with p-dimethylaminobenzaldehyde and also with thiophene-2- and selenophene-2-aldehydes can be used for identification of the corresponding tetraalkyl-3-furanidones.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

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# CATALYTIC ISOMERIZATION OF METHYLCYCLOPENTANE IN LIQUID HYDROGEN BROMIDE

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Equilibrium in the reaction of isomerization of methylcyclopentane (MCP) into cyclohexane (CH) has been studied in detail. It is known that aluminum halides do not catalyze it without a promoter. As was shown by Ipatieff, Pines, and others [1-5], isomerization of MCP is produced even by traces of olefin in the presence of hydrogen halides, but the latter do not themselves activate the reaction. This was explained by the fact that with olefins, hydrogen halides give alkyl halides which react further with aluminum halides by the equation



The formation of the carbonium ion initiates a chain process of isomerization which causes splitting of the methine hydrogen in the MCP molecule and its conversion into a carbonium ion,



Addition of benzene inhibits the reaction, since the carbonium ion ( $R^+$ ) is used in its alkylation.

In the present work hydrogen bromide was used not as an additive in catalysis of isomerization of MCP by aluminum bromide, but as the solvent in the liquid state. For the first time we had established the fact of isomerization of CH by a solution of aluminum bromide in liquid DBr by measuring the combination scattering spectrum in a study of the reaction of isotope exchange of CH hydrogen under these conditions [6].

We measured the rate of isomerization of MCP so as to compare it with the rate of exchange of hydrogen in MCP and CH with liquid DBr, which was practically the same in both hydrocarbons ( $k \cdot 10^3$  was  $1.2 \pm 0.7$  and  $1.5 \pm 0.7$ , respectively). We found that the rate of isomerization of MCP catalyzed by aluminum bromide was two orders higher ( $k \cdot 10^4 = 1.2$ ). The rate constant of isomerization of CH into MCP was also almost one and a half orders greater than the rate of the exchange reaction, since the equilibrium constant of isomerization was 7.5 at 27° [7]. Hence, in the exchange reaction there takes part an equilibrium mixture of MCP and CH independent of which of these hydrocarbons was taken for the experiment, and therefore the rate constants for the exchange are the same.

The question of the relation of rate of isomerization and deuterium exchange catalyzed by aluminum bromide has already been discussed in the literature [1]. The object of study was the system n-butane-AlBr<sub>3</sub>-DBr, where AlBr<sub>3</sub> and DBr occur in equivalent amounts, 10% of the number of moles of n-butane. In the absence of isomerization exchange was slight (6%), but it reached almost equilibrium value (92%) when by addition of 1% butene the isomerization reaction took place to 40%, that is, the ratio of rate of exchange and isomerization in the case of n-butane was the reverse of our work.

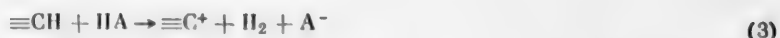
Previously [8] it was established by measurement of rate of isotopic exchange of hydrogen in benzene with liquid DBr that gallium bromide approaches aluminum bromide in catalytic activity. Because of the extreme sensitivity of this reaction to catalysis by these bromides we used them in weights on the order of decimilligrams. This limited the accuracy of measurement and did not permit us to determine surely the relative activity of aluminum bromide and gallium bromide. The values obtained here for the rate constant of isomerization of MCP catalyzed



by aluminum bromide and gallium bromide ( $k' \cdot 10^4 = 1.2$  and  $0.2$ , respectively) indicate a higher activity for the first of the bromides (by about 6 times) and agree with the results of recently published work of Russell [9].

Addition of cyclohexyl bromide to MCP (10% of the weight of MCP) hastens the isomerization reaction catalyzed by aluminum bromide by 8-10 times (Table 3). Such an effect agrees with the carbonium scheme for isomerization of MCP (equation 1); it is necessary only to introduce a correction that in liquid hydrogen bromide, a solvent with a low dielectric constant, there would hardly be formed free carbonium ions. They would take part very rapidly in the transition state (in reaction by equation 2) in a polarized complex of the type  $RBr \cdot AlBr_3$ . Brown [10] and Russell [9] also concluded that aluminum halides did not cause full ionization of the bond C-Hal in the catalytic reaction.

The question comes up of the mechanism of isomerization of MCP in liquid hydrogen bromide in the absence of a promoter. Nenitsecu [11] discussed the possibility of forming a carbonium ion of MCP by transfer of hydrogen from the MCP molecule in the form of a hydride ion combined with a proton of a strong acid (HA) with evolution of a molecule of hydrogen:



According to the results of Nenitsecu, MCP is isomerized as a result of a reaction in which the catalyst is aluminum halide, promoted by water, since aluminum halide hydrates are strong complex acids,  $HAIBr_3 \cdot OH$ . As was shown earlier [8] in experiments on acid catalysis of deuterium exchange, a solution of aluminum bromide in liquid hydrogen bromide is also a very strong proton acid. Therefore, we consider it possible that the scheme of Nenitsecu (with the above correction) is also applicable to the case of isomerization of MCP considered in our work. However, we must emphasize that direct evidence for the formation of molecular hydrogen has not been found.

#### EXPERIMENTAL

Preparations. MCP was kindly supplied to us by A. F. Plate, synthesized by the scheme:



The fraction to  $80^\circ$  was distilled in a column of 100 theoretical plates and methylcyclopentene was hydrogenated under pressure in the presence of Raney nickel catalyst at  $120^\circ$ . The catalyzate was distilled in a column and further purified by chromatography on silica gel,  $n_D^{20}$  1.4097.

Technical CH was boiled with a mixture of sulfuric and nitric acids. Then the hydrocarbon was washed, dried, and we collected the fraction  $78.9-80.0^\circ$  (749 mm), which was treated analogously, then distilled over metallic sodium, purified from traces of aromatic hydrocarbons by chromatography, distilled on an effective column, and we collected the fraction  $81.2-81.4^\circ$  (750 mm). The formalite reaction was negative,  $n_D^{20}$  1.4262.

The preparations of aluminum bromide and gallium bromide were obtained as previously described [8].

Method of carrying out the experiment. The method of taking a sample of hygroscopic bromides has been described [13], and the method of the experiment with liquid hydrogen bromide was discussed previously [8, 13]. Considering that, besides unsaturated hydrocarbons and alkyl halides as activators of the isomerization catalyzed by aluminum halides, water, bromine, and oxygen (in the light) can also be used, we took measures to exclude these contaminants. For the experiment we took 0.26-0.32 g of MCP. Per 0.09-0.44 g of aluminum bromide we took 13-30 g of hydrogen bromide, and per 0.1-0.4 g of gallium bromide we took 19-20 g of hydrogen bromide. The reaction mixture was kept in a thermostat ( $25 \pm 0.1^\circ$ ). Reaction was broken off by placing the ampule in liquid nitrogen; then we evaporated the hydrogen bromide, added 1 N alkali solution, separated the hydrocarbon, and twice distilled it over sodium.

Determination of the composition of the reaction mixture. The reaction product consisted of a mixture of MCP and CH. For determination of the composition of the mixture we used refractometric measurement, since the indexes of refraction of these hydrocarbons are quite different. The measurement was carried out on an Abbe refractometer at  $20^\circ$  with an accuracy of  $2 \cdot 5 \cdot 10^{-4}$ . For construction of the calibration curve we prepared four mixtures with different percent content of MCP: 8.4% ( $n_D^{20}$  1.4248), 21.2% ( $n_D^{20}$  1.4225), 41.6% ( $n_D^{20}$  1.4190), 70.0% ( $n_D^{20}$  1.4141). If on the graph we plotted the percent content of MCP mixed with CH against the index of refraction of the mixture, our results and those taken from work [14] lay on a common straight line.

TABLE 1  
Kinetics of Isomerization of Methylcyclopentane, Catalyst Aluminum Bromide

$C_K \cdot 10^3$	1.4	1.4	1.5	1.9*	2.0	2.1	2.2	2.4	3.0	6.6	6.9
$\tau$ (min)	180	60	30	60	97	135	34	60	109	30	60
$n_p^{20}$	1.4210	1.4168	1.4138	1.4178	1.4189	1.4221	1.4135	1.4182	1.4224	1.4194	1.4232
MCP (mole %)	30	54	71	48	42	23.5	73	46	21.5	39	17
$k \cdot 10^4$	1.5	2.1	2.2	2.5	3.0	3.5	1.8	2.6	3.4	6.6	8.0
$k' \cdot 10^1$	1.0	1.4	1.5	1.3	1.6	1.8	0.8	1.1	1.1	1.0	1.2

TABLE 2  
Kinetics of Isomerization of Methylcyclopentane, Catalyst Gallium Bromide

$C_K \cdot 10^3$	1.7	2.1	3.4	4.8
$\tau$ (hr)	3	6	6	6
$n_p^{20}$	1.4135	1.4160	1.4206	1.4223
MCP (mole %)	73	59	32	22
$k \cdot 10^4$	0.3	0.3	0.7	1.0
$k' \cdot 10^1$	0.2	(0.1)	0.2	0.2

TABLE 3  
Kinetics of Isomerization of Methylcyclopentane with Addition of Cyclohexylbromide, Catalyst Aluminum Bromide

$C_K \cdot 10^3$	0.7	1.0	1.3
$\tau$ (min)	30	30	30
$n_p^{20}$	1.4215	1.4230	1.4240
MCP (mole %)	38	30	23
$k \cdot 10^4$	7	9	12
$k' \cdot 10^1$	10	9	9

\* These experiments were carried out two years after the others.

Establishing the equilibrium composition of the isomeric mixture. The experiments on isomerization were carried out with both MCP and with CH, that is, equilibrium for the isomerization was reached from each side. About 0.3 g of hydrocarbon was dissolved in about 20 g of hydrogen bromide in the presence of 0.2 g of aluminum bromide, and the solution was kept for seven hours at 25°. Two experiments were run with each hydrocarbon. In all the experiments the mixture of hydrocarbons after purification had  $n_D^{20}$  1.4240, which corresponded to a content in it of 12.5 mole % of MCP and agreed fully with the literature data [14].

Measurement of the rate of isomerization. In Table 1 we give the results of experiments on isomerization of MCP catalyzed with  $AlBr_3$ , and in Table 2 we give the results of analogous experiments with  $GaBr_3$ .

The concentration of catalyst  $C_k$  was expressed in moles bromide per 1 mole liquid HBr,  $\tau$  was the duration of the experiment,  $k$  the rate constant of isomerization ( $\text{sec}^{-1}$ ), calculated from the equation  $k = \frac{2.3}{\tau} \lg \frac{C_0 - C_\infty}{C_\tau - C_\infty}$ , where  $C_0$ ,  $C_\tau$  and  $C_\infty$  correspond to concentrations of MCP at the beginning of the experiment ( $C_\infty = 100$  mole%), at the moment of time  $\tau$ , from the beginning (expressed in seconds), and on reaching equilibrium ( $C_\infty = 12.5$  mole%). In the last line of the tables we give the values of the relative rate constant of isomerization  $k'$ , which is a particular case of  $k$  at the concentration of the catalyst. Within the limits of error of the measurement we obtained a constant value for  $k'$ , from which it follows that the rate constant of isomerization is proportional to the concentration of the catalyst.

Effect of adding cyclohexyl bromide on rate of isomerization. Cyclohexyl bromide was prepared by solution of cyclohexene in liquid HBr and distillation in a vacuum ( $n_D^{20}$  1.4952). To  $0.3 \pm 0.01$  g of MCP was added  $0.03 \pm 0.0005$  g of cyclohexyl bromide. The reaction mixture after the experiment was treated with aqueous alkali and distilled over powdered sodium to constant index of refraction. In control experiments on such treatment the index of refraction of the mixture of MCP and cyclohexyl bromide of this composition fell from 1.4162 to 1.4110. Increase in index of refraction of the mixture due to loss of MCP in evaporation of HBr did not exceed 0.001. In the values for index of refraction of the reaction mixture we introduced a correction of -0.002. We obtained the result shown in Table 3.

#### SUMMARY

1. We have measured the kinetics of isomerization of methylcyclopentane into cyclohexane with catalysts of aluminum bromide and gallium bromide in a medium of liquid hydrogen bromide at 25°. We have shown that the rate constant of the reaction is proportional to the concentration of catalyst, and aluminum bromide is about six times more active than gallium bromide.
2. Addition of 10% cyclohexyl bromide to the methylcyclopentane hastens the isomerization reaction catalyzed by aluminum bromide 8-10 times.
3. We have found that the rate of isomerization of methylcyclopentane is two orders of magnitude greater than the rate of deuterium exchange with liquid DBr at equal concentrations of aluminum bromide.
4. We have suggested that isomerization of methylcyclopentane in liquid hydrogen bromide catalyzed by aluminum bromide (or gallium bromide) occurs by the same mechanism which Nenitsesku suggested for explaining the isomerization of methylcyclopentane catalyzed by aluminum halohydrate: the first step a chain reaction with conversion of methylcyclopentane into a carbonium ion due to splitting out of a hydride ion combined with the proton of a strong acid, which here can be the aluminum halohydrate and also the solution of aluminum bromide (or gallium bromide) in liquid hydrogen bromide.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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# A STUDY OF THE REACTIONS OF SOME ALKYL- AND ARYLALKOXY-SILANES WITH BORIC ACID

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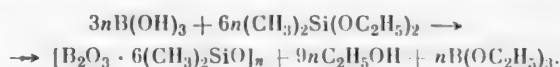
Original article submitted July 18, 1960

Among the organic silicon compounds the silicoboroorganic compounds are of great value and practical use. For the methods for preparing organic silicoboron compounds, besides the reaction of organic silicon compounds with inorganic compounds of boron ( $BBr_3$ ,  $BCl_3$ ,  $BF_3$ ,  $B_2H_6$ ,  $B_2H_5Br$ , etc.), there is the reaction of various alkyl (aryl) alkoxy- or halogenated silanes with boric acid. The attention of investigators has turned to the reaction of monofunctional organic silicon compounds with boric acid to give the possibility of synthesizing monomeric organic silicoboron compounds. Thus, Krieble [1] studied the reaction of trialkylalkoxysilanes with boric acid, finding formation of tris (trialkylsilyl) borate by the scheme



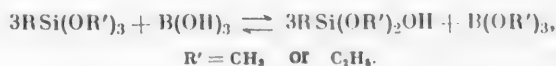
M. G. Voronkov and V. N. Zgonnik [2], in a test of the results of Krieble, established the dependence of yield of tris (trialkylsilyl) borate on the alkyl radical R used, and also obtained several new compounds by this method. Tris (trialkylsilyl) borates were also obtained by the reaction of trialkylsilanols [3,4], trialkylsilanes [3] and trialkylchlorosilanes [2] with boric acid.

In the reaction with boric acid of starting organic silicon compounds with the number of functional groups from two to four, polymeric organic silicoboron compounds were obtained. Thus, the reaction of tetraalkoxysilanes with boric acid gave monomeric and polymeric reaction products [5,6]. M. G. Voronkov and V. N. Zgonnik [2] studied the reaction with boric acid of dimethyldiethoxysilane, methyltriethoxysilane, and also dimethyldichlorosilane, and obtained dimethylpolysiloxane borate; the reaction of methyltriethoxysilane with boric acid led to formation of  $(B_2O_3 \cdot 4 CH_3SiO_{1.5})_n$ . Finally, reaction of dimethyldiethoxysilane with boric acid followed the scheme [2]

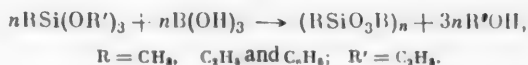


The resulting organic silicoboron compounds could be assigned the following formula:  $2 \{ [(CH_3)_2SiO_{1.5}]_n B \}_n$ .

A. P. Kreshkov and co-workers [6] found that at high temperatures alkyl (aryl) methoxy or ethoxysilanes react with boric acid with formation of methyl or ethyl esters of boric acid which color a flame green:



Our study showed that with careful heating of an equimolecular mixture of alkyl or aryltriethoxysilane with boric acid, ethyl alcohol distilled off with a small amount of ethyl borate, and a solid, polymeric organic silicoboron compound was formed (polyalkylsilylborate)

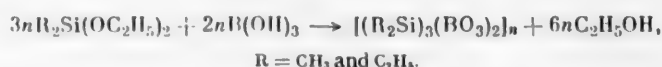


The following reaction took place along with the reaction described above:

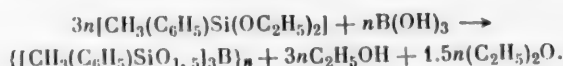


The reactions also took place in a medium of anhydrous organic solvents (toluene, benzene, etc.).

In the reaction of dimethyl- or diethyldiethoxysilane with boric acid we obtained dimethyl- and diethylpolysiloxane borate according to the scheme



However, the reaction of methylphenyldiethoxysilane with boric acid occurred differently:



As in the reactions described above, here also occurred formation of ethyl borate.

All the polymeric organic silicoboron compounds which we have synthesized were obtained for the first time, except for dimethylpolysiloxane borate, which was previously synthesized by M. G. Voronkov and V. N. Zgonnik [2] by another method.

#### EXPERIMENTAL

Methyltriethoxysilane (b.p. 141-145°,  $d_4^{20}$  0.8955,  $n_D^{20}$  1.3849) was synthesized [7, 8] from methyltrichlorosilane and anhydrous alcohol in the presence of aniline, which was used to bind the hydrogen chloride.

Ethyltriethoxysilane (b.p. 159°,  $d_4^{20}$  0.9207,  $n_D^{20}$  1.3853), phenyltriethoxysilane (b.p. 233-234°,  $d_4^{20}$  1.0133), dimethyldiethoxysilane (b.p. 111°,  $d_4^{20}$  0.890,  $n_D^{20}$  1.3839), diethyldiethoxysilane (b.p. 155-156°,  $d_4^{20}$  0.8752) and methylphenyldiethoxysilane (b.p. 221.5°,  $d_4^{20}$  0.9719,  $n_D^{20}$  1.4712) were synthesized [9] from the corresponding alkyl (aryl) chlorosilanes and anhydrous alcohol. The boric acid used was C.P.

The reaction of alkyl (aryl) triethoxysilanes with boric acid was carried out in a 10 ml pear-shaped flask fitted with a small Liebig condenser. The reaction mixture was heated on a glycerol bath to the temperature of the boiling point of alcohol; then as the alcohol distilled off and so did the other liquid products of the reaction, the temperature was slowly raised. After distillation the residue was dried to constant weight at 110-130°. The results of the experiments are given in Table 1.

The reactions of difunctionalalkyl and alkylarylalkoxysilanes with boric acid were carried out in an analogous manner. The results are given in Table 2.

The molecular weight of the resulting polymeric compounds of the type  $[(\text{R}_2\text{Si})_3(\text{BO}_3)_2]_n$  and  $\{[(\text{CH}_3)(\text{C}_6\text{H}_5)\text{SiO}_{1.5}]_3\text{B}\}_n$  was determined by the Rast method with benzoic acid. For all three compounds  $n \approx 8$ .

Elementary analysis was carried out by microcombustion using chromic oxide as the catalyst. Silicon was determined by the wet method [10]. Boron was determined as boric acid by titration with a 0.1 N solution of sodium hydroxide in the presence of mannitol.

A sample of the substance (about 0.1 g) was dissolved with boiling in an excess of alkali. After cooling the solution it was neutralized with 0.1 N hydrochloric acid to methyl red, mannitol was added, and the solution was titrated with 0.1 N sodium hydroxide solution with phenolphthalein [11].  $\text{B(OC}_2\text{H}_5)_3$  was determined in the distillate by the same method.

The compounds which we obtained were studied by qualitative functional analysis for the presence of hydroxyl [12] and ethoxyl [13] groups; we showed their complete absence. The characteristic infrared absorption maximum of the hydroxyl group at  $2.71 \mu$  [12] was absent.

Infrared spectra were taken on an IKS-6 spectrophotometer with a sodium chloride prism. The substances



TABLE 1

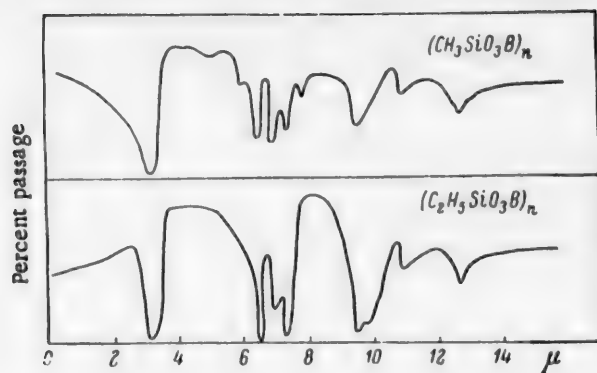
Data for the Reaction of Alkyl (aryl) triethoxysilanes with Boric Acid and Results of Analysis of Reaction Products at a Molar Ratio of Starting Compounds 1 : 1

Starting compounds (g)		Yield of (RSiO <sub>3</sub> ) <sub>n</sub> %	Amount of distillate (g)		Reaction product								Distillate of B(OC <sub>2</sub> H <sub>5</sub> ) <sub>3</sub> in % of starting B(OH) <sub>3</sub>
RSi(OC <sub>2</sub> H <sub>5</sub> ) <sub>3</sub>	B(OH) <sub>3</sub>		C <sub>2</sub> H <sub>5</sub> OH	B(OC <sub>2</sub> H <sub>5</sub> ) <sub>3</sub>	% B		% Si		% C		% H		
		found			calcu- lated	found	calcu- lated	found	calcu- lated	found	calcu- lated		
CH <sub>3</sub>	1.59	96.4	1.27	0.07	10.30, 10.40	10.60	27.10, 27.72	27.45	12.15, 11.81	11.75	3.79, 3.02	2.94	1.87
4.60 C <sub>2</sub> H <sub>5</sub>													
4.50 C <sub>2</sub> H <sub>5</sub>	1.43	93.4	2.30	0.10	9.45, 9.27	9.34	25.05, 24.31	24.20	20.65, 20.14	20.70	3.10, 3.41	3.13	2.80
5.00 C <sub>6</sub> H <sub>5</sub>													
1.28 5.00	1.28	97.2	2.12	0.05	6.12, 6.80	6.61	17.00, 17.51	17.05	43.90	3.24, 3.62	3.04	1.56	

TABLE 2

Data for the Reaction of Alkyl (aryl) diethoxysilanes with Boric Acid and Results of Analysis of the Reaction Product

Starting compounds (g)		Molar ratio	Yield of pro- duct, %	Amt. of distillate, g			Reaction product						Distillate of B(OC <sub>2</sub> H <sub>5</sub> ) <sub>3</sub> in % of starting B(OH) <sub>3</sub>	
R <sub>2</sub> Si(OR') <sub>2</sub>	B(OH) <sub>3</sub>			R'OH	R' <sub>2</sub> O	B(OR') <sub>3</sub>	% B		% Si		% C		% H	
						found	calcu- lated	found	calcu- lated	found	calcu- lated	found	calcu- lated	
CH <sub>3</sub> 2.56 C <sub>2</sub> H <sub>5</sub> 4.43	0.71	3 : 2	[R <sub>2</sub> Si] <sub>3</sub> (BO <sub>3</sub> ) <sub>2</sub> 96.5	1.58	—	0.07	7.29, 7.25	7.42	27.80, 28.05	28.80	22.47, 23.37	6.73, 6.72	6.22	
	1.03	3 : 2	[R <sub>2</sub> Si] <sub>3</sub> (BO <sub>3</sub> ) <sub>2</sub> 89.5	1.80	—	0.21	5.74, 6.32	5.76	22.05, 22.70	22.35	38.27, 38.51	7.90, 8.28	8.05	
	0.52	3 : 1	[R <sub>2</sub> SiO <sub>1.5</sub> ] <sub>3</sub> B 95.3	1.05	0.80	0.05	2.45, 2.40	2.44	19.30, 18.90	19.00	58.10, 56.80	5.44, 5.60	5.47	



were photographed in the form of tablets pressed with potassium bromide (1 g per 5 mg of polymer). As an example we give the infrared spectrum of the compounds  $(\text{CH}_3\text{SiO}_3\text{B})_n$  and  $(\text{C}_2\text{H}_5\text{SiO}_3\text{B})_n$ .

The spectra have absorption maxima characteristic of the following groups and bonds: 9.60 and 9.55  $\mu$  (Si-O), 7.40 and 7.30  $\mu$  (B-O), 12.75 and 12.70  $\mu$  (Si-CH<sub>3</sub>), 3.20, 3.15, and 6.50, 6.50  $\mu$  (C-H in CH<sub>3</sub>), which agree well with the literature [12,14].

X-ray analysis for all the compounds of type  $(\text{RSiO}_3\text{B})_n$  shows the absence of crystallinity.

#### SUMMARY

We have studied the reaction of methyltriethoxy-, ethyltriethoxy-, phenyltriethoxy-, dimethyldiethoxy-, diethyldiethoxy- and methylphenyldiethoxysilanes with boric acid. We have shown that these reactions go with formation of polymeric organic silicoboron compounds and are accompanied by evolution of alcohol and ethyl borate. We have obtained and studied for the first time by chemical and physical methods of analysis five polymeric organic silicoboron compounds:  $(\text{CH}_3\text{SiO}_3\text{B})_n$ ,  $(\text{C}_2\text{H}_5\text{SiO}_3\text{B})_n$ ,  $(\text{C}_6\text{H}_5\text{SiO}_3\text{B})_n$ ,  $[\text{C}_2\text{H}_5\text{Si}]_3(\text{BO}_3)_2$  and  $\{[(\text{CH}_3)(\text{C}_6\text{H}_5)\text{SiO}_{1.5}]_3\text{B}\}_n$ .

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# ALKYLATION OF BENZENE, TOLUENE AND XYLENE BY 1, 3-DIBROMOBUTANE

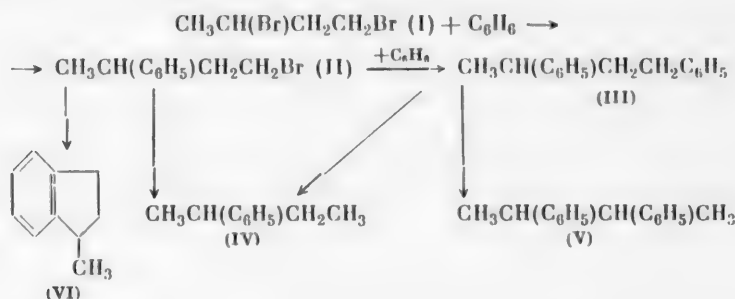
I. P. Tsukervanik and L. V. Bugrova

Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 7,  
pp. 2143-2149, July, 1961

Original article submitted July 11, 1960

In our previous work [1, 2] we showed that in the presence of aluminum chloride we could carry out a stepwise alkylation of benzene with 1, 3-chlorobromopropane. Here we obtained 3-(bromopropyl) benzene and 1, 3-diphenylpropane. In this work we suggested the possibility of the same stepwise alkylation with 1, 3-dibromobutane, expecting that the secondary bromine atom would react first.

We can assume that besides 4-bromo-2-phenylbutane (II) and 1,3-diphenylbutane (III) there will be secondary products formed: *sec*-butylbenzene (IV) on reduction of (II), 1-methylhydrindene by intramolecular cyclization of (II) and 2,3-diphenylbutane (V) by isomerization of (III).



Sisido and Nozaki [3] studied the condensation of 1,3-dichlorobutane with benzene in the presence of aluminum chloride. They were able to isolate only *sec*-butylbenzene (IV) and 2, 3-diphenylbutane (V). Schmerling and co-workers [4], however, showed the possibility of chloroalkylation of benzene by 1, 3-dichloro-3-methylbutane; they obtained 4-chloro-2-methyl-2-phenylbutane with a yield of 55%.

We carried out the condensation of 1, 3-dibromobutane with benzene under differing conditions (see table). With a minimum amount of aluminum chloride, at great excess of benzene, without heating, we succeeded in obtaining a high yield of 4-bromo-2-phenylbutane (II) (85%). Experiments carried out with a considerable amount of aluminum chloride (1-1.5 mole) on heating (50-80°) gave *sec*-butylbenzene (IV) and a mixture of diphenylbutanes (III, V). The yields of *sec*-butylbenzene reached 60%.

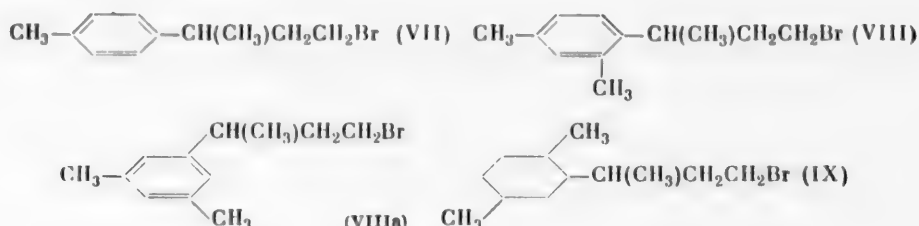
In none of our experiments could we detect 1-methylhydrindene (VI). This substance could not be isolated in the alkylation of benzene by 1, 3-dichlorobutane by the Japanese chemists [3].

Our attempts to obtain (VI) by treatment of (II) with aluminum chloride under conditions analogous to those described by Braun [5] did not give positive results. We obtained *sec*-butylbenzene (25%) and a high boiling substance which has not yet been studied.

The mixture of diphenylbutanes obtained in the condensation, to judge from the products of its oxidation, consisted of about equal amounts of (III) and (V). Sometimes a crystalline meso form of (V) resulted and was easily separated in the pure state.

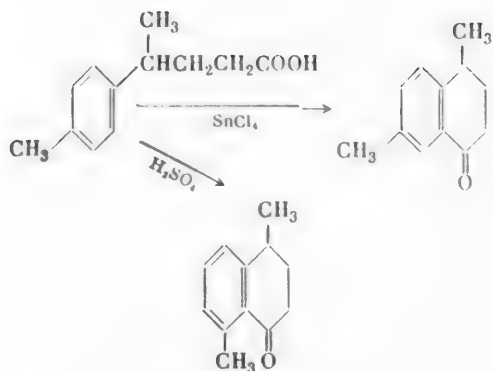
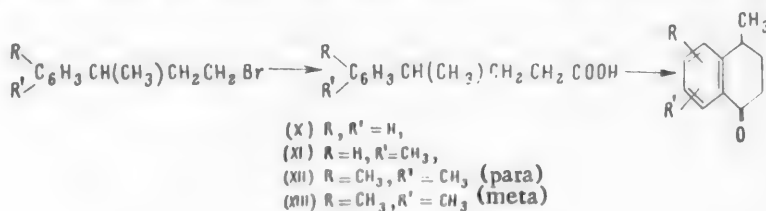
By analogy with the earlier studied reaction with 1,3-chlorobromopropane [2] we considered that the *sec*-butylbenzene (IV) was obtained by reduction of (II) and also by splitting of diphenylbutanes (III, V) with aluminum

Then we studied the alkylation by 1, 3-dibromobutane of toluene, p- and m-xylene under conditions most favorable for obtaining the products of bromoalkylation. We obtained the undescribed 4-bromo-2-(p-tolyl)butane (VII) (75%), 4-bromo-2-(m-xylyl)butane (VIII) (45%), [possibly admixed with isomer (VIIIa)] and 4-bromo-2-(p-xylyl)butane (IX) (30%).



Thus, in this series of reactions we have shown the possibility of stepwise alkylation by dihalogen compounds due to the great activity of the secondary bromine atom. These results supplement the earlier data from our laboratory on alkylation by diols, where the secondary hydroxyl reacts much more easily [6].

For identification of the synthesized bromobutylbenzenes (II, VII, VIII, IX), they were converted by the Grignard reaction into the corresponding arylvaleric acids, which were cyclized into tetralones described in the literature.



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# EXPERIMENTAL

1, 3-Dibromobutane was obtained from 1, 3-butandiol by the action of phosphorus tribromide [9]; we used the preparation with b.p. 170-172° (730 mm),  $n_D^{20}$  1.5092. The anhydrous aluminum chloride was the commercial, marked "pure". The copper powder was obtained by reduction of a solution of copper sulfate with zinc dust [10].

Alkylation was carried out by stepwise addition of aluminum chloride to a solution of 1, 3-dibromobutane in the aromatic hydrocarbon. The mixture was stirred with a mechanical stirrer in ordinary apparatus.

We give the results of several typical experiments with benzene in the table.

4-Bromo-2-phenylbutane (II). The crude product with b.p. 110-112° (11 mm) was fractionated on a column: b.p. 110.5° (10 mm),  $d_4^{19}$  1.2720,  $n_D^{19}$  1.5381,  $MR_D$  52.52. The literature gives [11] b.p. 108-110° (8 mm).

Found%: Br 37.27.  $C_{10}H_{13}Br$ . Calculated %: Br 37.51.

By the Grignard reaction we synthesized from substance (II) 4-phenylvaleric acid (X). Yield 62%, B.p. 165° (12 mm); amide m.p. 63-64°. The literature [11] gives b. p. 170° (10 mm).

Alkylation of Benzene by 1, 3-Dibromobutane (I). Reaction Carried out with 0.05-0.1 Mole 1, 3-Dibromobutane

Molar ratio benzene: 1,3- dibromobutane: aluminum Cl	Temp. and duration		Yield, %			
	stirring of mixture (hr)	standing of mixture (hr)	(I)	(II)	(III+V)	(IV)
10 : 1 : 0.1	15°; 2	18-20°; 44	55	30	—	—
10 : 1 : 0.1	10; 9	16-18; 15	35	50	—	—
10 : 1 : 0.1	10; 12	18-20; 14	—	85	—	—
12 : 1 : 1	6; 2	16-18; 46	16	—	32	43
20 : 1 : 1.5	20; 2.5	50-60; 2	—	—	23	30*
10 : 1 : 1	20; 15	80	6	—	6	60*

\* Much tar.

We carried out cyclization of the acid with aluminum chloride [12]. We obtained 1-methyl-3-tetralone with b. p. 130-131° (10 mm); semicarbazone m.p. 205-206°. The literature [12] gives b.p. 133-134° (12 mm); semicarbazone m.p. 210-211°.

Acid (X) was also obtained by oxidation of 4-phenyl-1-pentanol [13]. The 1-methyl-3-tetralone obtained from it gave a semicarbazone with m.p. 205-206°, identical with the preceding.

By the action of potassium cyanide on substance (II) [14] we obtained the nitrile with b.p. 125-126° (12 mm). The literature [15] gives b.p. 125-126° (12 mm). Its hydrolysis by concentrated hydrochloric acid at 120-130° in a sealed tube for 20 hours gave acid (X), which gave an amide with m.p. 63.5-64° (from alcohol).

sec-Butylbenzene [16] was isolated from the fraction with b.p. 68-72° (30 mm) by repeated distillation over sodium. B.p. 172-173° (730 mm),  $n_D^{20}$  1.4890,  $d_4^{20}$  0.8636. The acetamino derivative melted at 123-124°. The literature [17] gives m.p. 126°.

Mixture of diphenylbutanes (III, V). B. p. 288-291° (790 mm),  $n_D^{20}$  1.5535,  $d_4^{20}$  0.9750. The crystals of (V) which separated from the oil had m.p. 125.5-126° (from alcohol), which corresponded to meso-2, 3-diphenylbutane. The literature [16] gives m. p. 126°. We oxidized 0.8 g of the mixture of (III, V) with 2.8 g of potassium dichromate in 21 ml of 80% acetic acid by heating in a water bath for ten hours. We isolated: acetophenone (0.3 g) with b. p. 86-88° (20 mm) (semicarbazone m. p. 196°, 2, 4-dinitrophenylhydrazone m. p. 248°); phenylacetaldehyde (0.1 g) with b. p. 98-100° (20 mm) (semicarbazone m. p. 152°, 2, 4-dinitrophenylhydrazone m. p. 120-119°, which corresponded to the data in the literature [18]).

Condensation of (II) with benzene. Ratio of reagents (II):  $AlCl_3$  :  $C_6H_6$  = 1 : 1 : 10. The mixture was kept at 80° for 1.5 hours, then left at room temperature for 30.5 hours. After the usual treatment and distillation we isolated

a butylbenzene fraction with b. p. 172-176° 0.6 g (49%) and a diphenylbutane fraction with b. p. 225-230° (90 mm) 80 g (38%), an oil with crystals; some tar was left.

Condensation of (II) with benzene under milder conditions at a ratio (II) :  $\text{AlCl}_3$  :  $\text{C}_6\text{H}_6$  = 1:0.5:10 at 20-22° for 72 hours gave 45% of sec-butylbenzene and 30% of a mixture of 1, 3- and 2, 3- diphenylbutanes.

To 0.7 g of a mixture of diphenylbutanes (III, V) in a solution of 5 ml of benzene was added 0.22 g of aluminum chloride and it was left at 20-22° for 45 hours. After the usual treatment we isolated sec-butylbenzene 0.35 g (71%) and 2, 3-diphenylbutane 0.12 g (17%). Some black tar.

Attempt to cyclize (II) into methylhydrindene [5]. To a mixture of 4 g of (II) in 25 ml of ligroin was added 4 g of aluminum chloride during one hour. The mixture was heated to 50-60° for five hours. As a result of distillation we separated sec-butylbenzene 0.5 g (25%) and a thick oil with crystals 0.6 g.

Condensation of (I) with toluene. To a solution of 10.8 g (0.05 mole) of 1, 3-dibromobutane in 60 ml (0.6 mole) of toluene with stirring was added in the course of two hours 0.66 g (0.005 mole) of aluminum chloride. The temperature of the mixture was kept between 10-12° by cooling with water. The mixture stood for eight hours at 18-20°. After the usual treatment and fractionation we isolated 8.45 g (75%) of 4-bromo-2(p-tolyl) butane (VII) with b.p. 126.5-129° (11 mm).

4-Bromo-2-(p-tolyl) butane (VII) after repeated distillations from a column with a long rectifying column had b.p. 127.5-128° (13 mm).

$d_4^{10}$  1.2328,  $n_D^{19}$  1.5363,  $M_{rD}$  57.31. Calc. 57.42.  
Found %: Br 35.08.  $\text{C}_{11}\text{H}_{15}\text{Br}$ . Calculated %: Br 35.24.

On oxidation of 0.5 g of (VII) with 10 ml of nitric acid (d 1.1) in a sealed tube at 160° for 18 hours we obtained 0.345 g (94%) of terephthalic acid. Its dimethyl ester had m. p. 140-141° (from alcohol). The literature [23] gives m. p. 140-141°.

By the Grignard reaction we obtained 4-(p-tolyl) valeric acid (XI) with b.p. 177-178° (12 mm). The literature [19,20] gives 178-180° (15 mm); 173-174° (9 mm). By heating 0.9 g of (XI) with 5 ml of 80% sulfuric acid for six hours on a water bath [21] we obtained 0.54 g of 4, 6-dimethyl-1-tetralone with b. p. 132-134° (5 mm); semicarbazone m. p. 221-222°, 2, 4-dinitrophenylhydrazone m. p. 203-204°. The literature [22] gives b. p. 108-110° (1 mm); semicarbazone m. p. 220-221°; 2, 4-dinitrophenylhydrazone m. p. 203-204°.

The reaction was repeated with known acid (XI) obtained by oxidation of 4- (p-tolyl)-1-pentanol [13] under the same conditions. We obtained the identical 4, 6-dimethyl-1-tetralone.

Condensation with p-xylene was carried out under the same conditions as for toluene, with 10.8 g (0.05 mole) of 1, 3-dibromobutane, 62 ml (0.5 mole) of p-xylene, and 0.66 g (0.005 mole) of aluminum chloride. After two hour stirring, the mixture stood for 22 hours at 18-20°. We obtained 3.6 g (45%) of 4-bromo-2-(p-xylyl) butane (IX) with b. p. 133-136° (13 mm). Repeated distillation gave a colorless oil with a pleasant odor.

b. p. 135-136° (13 mm),  $d_4^{19}$  1.5361,  $M_{rD}$  62.07. Calc. 61.95.  
Found %: Br 33.01.  $\text{C}_{12}\text{H}_{17}\text{Br}$ . Calculated %: Br 33.19.

By oxidation with nitric acid (d 1.1) (16 hours at 160°C in a sealed tube) we obtained trimellitic acid with m.p. 230-235°C; after its sublimation in a vacuum we obtained the anhydro acid with m. p. 162.5-163°C. The literature [24] gives m. p. 162.5-163°C. From 0.3 g of acid, 3 ml of methanol and 3 drops of concentrated hydrochloric acid after ten-hour standing of the mixture we isolated 0.22 g of methyl ester of trimellitic acid with m.p. 177°C. The literature [24] gives m.p. 177°C.

From (VIII) by the Grignard reaction we obtained 4-(2,5-dimethylphenyl) valeric acid (XII) with b. p. 150-152° (4 mm); after long standing it crystallized; m.p. 105.5-106.5°. The literature [8] gives b. p. 126-128° (0.15 mm); m. p. 109-111°. A mixed sample with acid (XII) obtained by oxidizing 4-(2, 5-dimethylphenyl)-1-pentanol [13] gave no melting point depression. The amide of acid (XII) melted at 90-91.5°. The literature [8] gives m. p. 92-91.5°.

Condensation of m-xylene. From 5.4 g (0.025 mole) of 1, 3-dibromobutane, 30 ml (0.3 mole) of m-xylene and 0.33 g (0.0025 mole) of aluminum chloride after two-hour stirring (10-12°) and 46-hour standing we obtained 2 g (30%) of 4-bromo-2-(m-xylyl)butane (VIII) with b. p. 122-122.5° (7 mm).



$d_4^{20}$  1.1725,  $n_D^{20}$  1.5290,  $M_{rD}$  62.16; calc. 61.95.

Oxidation by nitric acid as described above gave trimellitic acid (with a slight admixture of trimesic acid) with m. p. 360°. The literature [25] gives m. p. about 360° (with decomposition).

From substance (VIII) by the Grignard reaction we obtained 4-(2,4-dimethylphenyl) valeric acid (XIII) with b. p. 183-185° (3 mm). The literature [8] gives b. p. 140° (0.5 mm).

Acid(XIII) in chloroform solution was treated on a water bath for 0.5 hours with phosphorus pentachloride. The crude acid chloride after removal of solvent and excess phosphorous pentachloride in a vacuum was treated with tin chloride in benzene (shaking at 20°, 10-hour standing, 2-hour heating on a water bath). We obtained 4, 5, 7-trimethyltetralone with b. p. 150-152° (6 mm); semicarbazone m. p. 221-222°; 2, 4-dinitrophenylhydrazones m.p. 231-232°. The literature [8] gives b. p. 174-176° (20 mm); semicarbazone m. p. 221.6-222.4°; 2, 4-dinitrophenylhydrazones m. p. 231-232.5°.

Condensation of substance (I) with benzene and toluene in the presence of freshly precipitated copper. A mixture of 10.8 g of (I) in 20 ml of benzene and 0.32 g of freshly precipitated copper was heated for seven hours at 180° in a sealed tube. After distillation we obtained 6.1 g (57%) of unreacted (I) and 1.8 g (36%) of 4-bromo-2-phenylbutane (II).

With toluene the condensation was carried out at ratio (II): Cu:  $CH_3C_6H_5$  = 1:0.005:20 by heating on gauze for 40 hours. We obtained 2.2 g (30%) of 4-bromo-2-(p-tolyl)butane (VIII).

#### SUMMARY

1. We have shown the possibility of bromobutylation of benzene, toluene and xylene (p- and m-) when they are condensed with 1, 3-di-bromobutane in the presence of aluminum chloride and freshly precipitated copper.

2. For the first time we have described 4-bromo-2-(p-tolyl)butane (VII), 4-bromo-2-(p-xylyl)butane (IX) and 4-bromo-2-(m-xylyl)butane (VIII) and have studied their transformations into the corresponding arylvaleric acids and tetralones.

3. We have shown that the regularities in the course of condensation of 1,3-dibromobutane with aromatic hydrocarbons depending on conditions are the same as were previously found for condensation of diatomic alcohols.

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# CYCLOALKYLATION OF AROMATIC COMPOUNDS

## XVIII. THE REACTION OF BENZENE

### WITH 4-CYCLOHEXYLCYCLOHEXANOL

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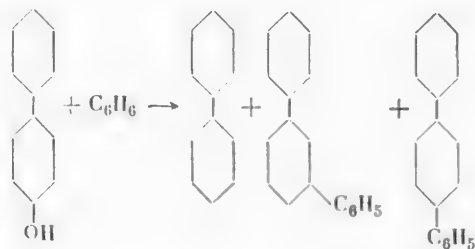
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Reports have been published of the differing isomerizing abilities of sulfuric acid and aluminum chloride in the alkylation of aromatic compounds. According to Schmerling and others [1], only secondary alkylbenzenes are formed in presence of aluminum chloride. This view was supported by the work of Friedmann, Morritz and Morrissey [2], who studied the alkylation of benzene and some of its homologs by methylcyclohexenes. On the other hand they found, as did Linsk [3], that in presence of sulfuric acid the sole product is tert-(methylcyclohexyl)benzene. The same product was obtained by alkylation of benzene with 1-chloro-1-methylcyclohexane in presence of sulfuric acid [4]. One of us [5], however, also obtained tert-(methylcyclohexyl)benzene as the main product when benzene was condensed with 1-methylcyclohexanol in presence of aluminum chloride. It was of interest to compare the isomerizing ability of these two catalysts in the case of more complex cyclic alcohols.

We studied the alkylation of benzene with 4-cyclohexylcyclohexanol in presence of aluminum chloride and concentrated sulfuric acid. The alkylation of aromatic compounds by dicyclohexyl derivatives has been little studied. By reacting benzene with 4-bromodicyclohexyl in presence of aluminum chloride, Braun and others [6] obtained a small quantity of cyclohexylcyclohexene and two monoalkylation products—(3-dicyclohexyl)- and (4-dicyclohexyl)benzene, the first of these predominating. These hydrocarbons were not isolated in the pure form but were identified by dehydrogenation to terphenyls. Alkylation of some aromatic compounds by 4-cyclohexylcyclohexanol in presence of boron fluoride etherate has been described by Fieser and co-workers [7], who obtained substances containing the trans-4-cyclohexylcyclohexyl group. The product of condensation of the same alcohol with  $\beta$ -naphthol in presence of sulfuric acid had even earlier been described [8] as 1-(4-dicyclohexyl)-2-naphthol. Less definite results were obtained by Monteils [9] in the alkylation of benzene and chlorobenzene with 1-cyclohexyl-dicyclohexene in presence of ferric chloride. He did not establish the structure of the isolated products. The reaction of 2-cyclohexylcyclohexanol with phenol in presence of phosphorus pentoxide has also been described. The authors believed [10] that the reaction product was o-(2-dicyclohexyl)phenol.

The products of our condensation of a mixture of stereoisomeric 4-cyclohexylcyclohexanols with benzene in presence of aluminum chloride were dicyclohexyl (with a trace of cyclohexylcyclohexene), (3-dicyclohexyl)benzene and (4-dicyclohexyl)benzene.



The reaction goes most satisfactorily with equimolar quantities of alcohol and catalyst in a large excess of benzene with prolonged heating, at first at 40-50° and later at 80-85° [11]. Under these conditions 61-73% of

monoalkylated product, 10-14% of dialkylated product, 10-12% of dicyclohexyl and a little cyclohexylcyclohexene were obtained. With a smaller quantity of aluminum chloride the yield of dicyclohexyl was nearly the same, but that of (dicyclohexyl)benzenes decreased. Reaction under more drastic conditions (smaller quantity of benzene and higher temperature) gave a considerable amount (33.7%) of dicyclohexyl and a lower yield (31.4%) of (dicyclohexyl)benzenes.

In all cases the monoalkylated product was a mixture of 75-80% of (3-dicyclohexyl) benzene and 20-25% of (4-dicyclohexyl)benzene, which were separated by freezing. Their structure was confirmed by hydrogenation and dehydrogenation to known substances. The (dicyclohexyl) benzenes were characterized by preparation of crystalline derivatives.

The same products were obtained by taking pure trans-4-cyclohexylcyclohexanol into reaction. In this case, however, the yield of dicyclohexyl was far higher and that of (dicyclohexyl) benzenes correspondingly lower than from a mixture of the stereoisomeric alcohols under the same conditions.

Reaction in presence of sulfuric acid gave the same products of alkylation—(3-dicyclohexyl)- and (4-dicyclohexyl) benzenes—but with a somewhat higher content of the latter. In contrast, however, to the reaction in presence of aluminum chloride, the resulting low-boiling product contained, apart from dicyclohexyl and cyclohexylcyclohexene, a small quantity of phenylcyclohexane or diphenyl (on dehydrogenation it was wholly converted into diphenyl). The reaction course with sulfuric acid depended on the quantity of catalyst and the temperature (Table 2). With a small quantity of sulfuric acid the main product was dicyclohexyl regardless of the temperature; an increase in the quantity of sulfuric acid led to a fall in the yield of dicyclohexyl. On the other hand the yield of (dicyclohexyl) benzenes increased with increasing quantity of catalyst and with rising temperature.

The results give the impression that dicyclohexyl may be formed before the (dicyclohexyl) benzenes and is subsequently converted into the latter by interaction with benzene. This hypothesis was not supported, however, by experiment. Dicyclohexyl was recovered unchanged after being stirred with benzene and sulfuric acid at 18-20° for 5 hr. Heating of dicyclohexyl with benzene and aluminum chloride at 80-85° for 9 hr also did not give (dicyclohexyl) benzenes, although in this case a considerable proportion of the dicyclohexyl underwent change. No essential difference between aluminum chloride and sulfuric acid accordingly exists in this reaction. The same alkylation products were obtained with the two catalysts; the secondary products alone were slightly different.

#### EXPERIMENTAL

4-Cyclohexylcyclohexanol. Condensation of phenol with cyclohexanol in presence of orthophosphoric acid [12] gave a mixture of o- and p-cyclohexylphenols which were separated via the phenates. Yields were 32% of o-cyclohexylphenol and 34% of p-cyclohexylphenol (referred to the theoretical yields). Crude p-cyclohexylphenol melted at 126°. It was hydrogenated in a rotating autoclave in presence of Raney nickel (10%) at 180° and 90 atm hydrogen pressure. Hydrogenation was conducted in alcoholic solution. After completion of hydrogenation, the content of the autoclave was extracted with benzene, and the benzene solution was filtered through a layer of fibrous asbestos into a distillation flask. The benzene and alcohol were taken off and 4-cyclohexylcyclohexanol was left as a mixture of the cis- and trans-forms. After recrystallization from alcohol the mixture melted at 83-91°. This mixture was used in the majority of reactions. Numerous crystallizations from alcohol led to isolation of pure trans-isomer in the form of needles with m.p. 104-104.5°. Literature [13]: m.p. 103-104°.

#### Alkylation of Benzene with 4-Cyclohexylcyclohexanol in Presence of Aluminum Chloride.

Condensation was performed by the usual method [14]. After the aluminum chloride had been added, the reaction mixture was most usually allowed to stand at room temperature until the next day, and then heated until hydrogen chloride was no longer evolved. After completion of the reaction, the mixture was washed first with dilute hydrochloric acid and then with warm sulfuric acid (d 1.76) for elimination of olefins and unreacted alcohol. Cold concentrated acid was used in some experiments, but then the benzene was previously distilled off. The product was afterward washed with water and dried before fractionation over sodium. Dicyclohexyl came over at 105-107° (6 mm), (dicyclohexyl) benzenes at 180-190° (9 mm) and disubstituted products at 230-250° (2 mm). Conditions and results of condensations are set forth in Table 1. In all experiments 9.12 g (0.05 mole) of 4-cyclohexylcyclohexanol was taken into reaction.

Pure trans-4-cyclohexylcyclohexanol was used in the last experiment.

The products were purified by redistillation.

TABLE 1

Alkylation of Benzene with 4-Cyclohexylcyclohexanol in Presence of Aluminum Chloride

Molar ratio $C_6H_{11}C_6H_{10}OH$ : $AlCl_3 : C_6H_6$	Reaction conditions			Yields, %		
	standing at 15-20° (days)	heating (hr)	tem- perature	dicyclo- hexyl	dicyclo- hexyl) benzenes	disubstituted products
1 : 0.73 : 28	1	10	80-85°	14.6	6.6	—
1 : 0.85 : 46	1	10	80-85	13.4	25.8	—
1 : 1 : 46	1	10	80-85	12.8	71.5	13.7
1 : 1 : 46	6	15	40-85	12.2	72.7	13.7
1 : 1 : 9	—	15	85	33.7	31.4	16.0
1 : 1 : 46	1	15	40-85	20.5	50.4	10.0

Dicyclohexyl:B.p. 105-107° (6 mm),  $n_D^{20}$  1.4790,  $d_4^{20}$  0.8885,  $MR_D$  53.08, Calculated 53.22.Dicyclohexyl prepared from trans-4-cyclohexylcyclohexanol had b. p. 78-80° (2 mm),  $n_D^{20}$  1.4800. Literature [15]: b. p. 238.5°;  $n_D^{20}$  1.4800,  $d_4^{20}$  0.8860.

Dehydrogenation of dicyclohexyl in a flow system over platinized carbon (10% Pt) at 300-320°C in a hydrogen stream [16] gave diphenyl with m.p. 67°C. It melted at 69°C (from alcohol). A mixture with a known sample of diphenyl did not give a melting point depression.

(Dicyclohexyl) benzenes, B.p. 155-160° (3 mm),  $n_D^{20}$  1.5346-1.5360. The resulting fractions partly crystallized on standing. For separation of the crystals, the mixture was dissolved in an equal volume of absolute ether and the solution kept for 2-3 hr in solid carbon dioxide. The precipitated crystals were suction-filtered on a glass filter also cooled with solid carbon dioxide, and washed with a small quantity of cooled ether. In this way 20-25% of crystalline (4-dicyclohexyl) benzene was obtained from products of different condensations (including also the condensation of trans-4-cyclohexyldicyclohexanol).

(3-Dicyclohexyl) benzene was isolated from the residual liquid after separation of the crystals. This was done by distillation over sodium:

B. p. 158-160° (3 mm), 173-175° (6 mm),  $n_D^{20}$  1.5322,  $d_4^{20}$  0.9736,  $MR_D$  77.17, Calculated 77.32.Found%: C 89.06; H 10.56  $C_{18}H_{26}$ . Calculated %: C 89.19; H 10.81.

Nitration of 2 g of the hydrocarbon with 7 ml of nitrating mixture for several minutes, firstly at room temperature and then at 30-40°, gave 2.1 g (90%) of nitro compound which distilled at 190-210° (5 mm). Its oxidation with dilute nitric acid (d 1.1) in a sealed tube at 130-150° gave p-nitrobenzoic acid with m. p. 240°. The nitro compound was reduced with tin and hydrochloric acid, and the resulting amine was acetylated and benzoylated.

p-(3-Dicyclohexyl) acetanilide crystallized from dilute alcohol in the form of rectangular plates or of leaflets with m. p. 167-168°.Found %: N 5.06,  $C_{20}H_{29}ON$ . Calculated %: N 4.68.p-(3-Dicyclohexyl) benzanilide crystallized from alcohol in the form of small needles with m. p. 174-175°.Found %: N. 3.99,  $C_{25}H_{31}ON$ . Calculated %: N 3.88.

Dehydrogenation of (3-dicyclohexyl) benzene by heating with 20% platinized carbon in a test tube (with a side tube for discharge of gases) at 300-310° until the content completely solidified gave m-terphenyl with m.p. 87° (from alcohol).

m-Terphenyl was also obtained when (3-dicyclohexyl) benzene was boiled with an equal amount of selenium until hydrogen selenide ceased to come off. The product was extracted with benzene, the benzene solution was

passed through an activated carbon column; the benzene was evaporated, and the residue recrystallized from alcohol; m. p. 87°. Neither of the two specimens of m-terphenyl gave a depression of melting point in admixture with authentic m-terphenyl.

Hydrogenation of (3-dicyclohexyl) benzene over Raney nickel (10% of the hydrocarbon weight) at 180° and 100 atm hydrogen pressure gave a mixture of stereoisomeric 1, 3-dicyclohexylcyclohexanes. These were separated by freezing of the ethereal solution in solid carbon dioxide. The solid isomer melted at 65° (from alcohol). According to the literature [17] the solid stereoisomer of 1, 3-dicyclohexylcyclohexane melts at 66-67°.

The liquid stereoisomer remaining after the freezing operation was distilled over sodium:

B. p. 145° (3 mm),  $n_D^{20}$  1.5020,  $d_4^{20}$  0.9332,  $MR_D$  78.56; calculated 78.82. Literature data [18]: b. p. 211-215° (39 mm),  $n_D^{20}$  1.5038,  $d_4^{20}$  0.935.

(4-Dicyclohexyl) benzene. Crystallized from absolute alcohol in the form of colorless plates with m. p. 84-84.5°.

Literature data [6]: m. p. 86°

Found %: C 89.03; H 10.57.  $C_{18}H_{26}$  Calculated %: C 89.19; H 10.81.

Nitration of 2 g of the hydrocarbon dissolved in 30 ml of glacial acetic acid with 20 ml of fuming nitric acid (d 1.5) at first in the cold and then with heating to 60° gave 1.9 g (80%) of p-(4-dicyclohexyl) nitrobenzene in the form of colorless, elongated plates with m. p. 117-118° (from alcohol).

Found %: N 5.22; 4.97.  $C_{18}H_{26}O_2N$ . Calculated %: N 4.87.

Oxidation with dilute nitric acid in a sealed tube at 130-150° gave p-nitrobenzoic acid with m. p. 240°. The nitro compound was reduced with tin and hydrochloric acid, and the resulting amine was acetylated and benzoylated.

p-(4-Dicyclohexyl) acetanilide forms lustrous leaflets with m. p. 217° (from alcohol).

Found %: N 4.86, 4.94.  $C_{20}H_{28}ON$ . Calculated %: N 4.68.

p-(4-Dicyclohexyl) benzanilide forms fine, small needles with m. p. 249-250° (from a mixture of alcohol and benzene).

Found %: N 4.14, 4.08.  $C_{25}H_{31}ON$ . Calculated %: N 3.88.

Nitration of 0.5 g of (4-dicyclohexyl) benzene with 5 ml of nitrating mixture, at first at room temperature and then with heating on a warm water bath for 4-5 minutes until a homogeneous solution had formed, gave 0.48 g (70%) of 1-(4-dicyclohexyl)-2, 4-dinitrobenzene in the form of yellow, small needles with m. p. 144-145° (from alcohol).

Found %: N 8.12, 8.26.  $C_{18}H_{24}O_4N_2$ . Calculated %: N 8.42.

From the filtrate was isolated a small quantity of p-(4-cyclohexyl) nitrobenzene with m. p. 117°.

Dehydrogenation of (4-dicyclohexyl) benzene by heating with selenium until hydrogen selenide ceased to be evolved gave p-terphenyl with m. p. 212-213°. p-Terphenyl with the same melting point was obtained by boiling (4-dicyclohexyl) benzene with 20% platinized carbon until hydrogen was no longer evolved. Mixed melting point tests on each of the specimens with authentic p-terphenyl did not give depressions.

Hydrogenation of (4-dicyclohexyl) benzene over Raney nickel under hydrogen pressure gave a mixture of the stereoisomeric 1, 4-dicyclohexylcyclohexanes. The trans-form (m. p. 163°) and the cis-form (m. p. 53°) were isolated by crystallization from alcohol and acetone. According to the literature [6, 17] trans-1, 4-dicyclohexylcyclohexane melts at 162° and cis-1, 4-dicyclohexylcyclohexane at 55-57°.

#### Alkylation of Benzene with 4-Cyclohexylcyclohexanol in Presence of Sulfuric Acid

Reactions were performed in a three-necked flask with mechanical stirring. A mixture of benzene and 4-cyclohexylcyclohexanol (mixture of stereoisomers) was added at a definite temperature to concentrated sulfuric acid in the course of 1-1.5 hr, after which stirring was continued at the same temperature for another 2-3 hr. The benzene layer was then separated and washed with a fresh portion of sulfuric acid. The products were then isolated as

described earlier. Results of condensations under various conditions are set forth in Table 2. In all experiments 9.12 g (0.05 mole) of 4-cyclohexylcyclohexanol was taken into reaction.

The first fraction of the reaction product had the following constants after a second washing with sulfuric acid and distillation over sodium: b. p. 60-61° (1 mm),  $n_D^{20}$  1.4920,  $d_4^{20}$  0.9060. It differed appreciably from dicyclohexyl in properties. Dehydrogenation in a flow system over platinized carbon at 324-340° in a hydrogen stream gave diphenyl which melted (without any purification) at 68°.

TABLE 2  
Alkylation of Benzene with 4-Cyclohexylcyclohexanol in Presence of Sulfuric Acid

Molar ratio $C_6H_{11}C_6H_{10}OH:$ $H_2SO_4 : C_6H_6$	Reaction conditions		Yield, %	
	tempera- ture	duration (hr)	dicyclo- hexyl	(dicyclo- hexyl)ben- zenes
1 : 2.8 : 33	-5 - 0°	3.5	19.0	12.5
1 : 2.8 : 33	0 - 6	4	25.9	10.7
1 : 2.8 : 33	10-13	3.5	25.7	9.5
1 : 2.8 : 33	14-15	3.5	27.0	6.0
1 : 13 : 33	-5 - 0	9	9.1	13.3
1 : 19 : 33	10-22	4.5	13.2	53.8
1 : 17 : 25	24-32	5	9.0	43.0

The second fraction consisted mainly of (3-dicyclohexyl) benzene and a small quantity of (4-dicyclohexyl) benzene. It did not crystallize even after prolonged standing: b. p. 134-135° (0.5 mm),  $n_D^{20}$  1.5350,  $d_4^{20}$  0.9763. Dehydrogenation over platinized carbon gave m- and p-terphenyls.

It was converted by the usual method into the acetamino derivative with m. p. 168° and the benzamino derivative with m. p. 175°; these were identical with the corresponding derivatives of (3-dicyclohexyl) benzene.

#### SUMMARY

Reaction of 4-cyclohexylcyclohexanol with benzene in presence of aluminum chloride and sulfuric acid leads to the same products of alkylation—(3-dicyclohexyl)- and (4-dicyclohexyl) benzenes. In both cases (3-dicyclohexyl)-benzene is the main product, but more of it is formed in presence of sulfuric acid. In both cases dicyclohexyl is another product, while with sulfuric acid a small quantity of phenylcyclohexane or diphenyl is also formed.

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## CYCLOALKYLATION OF AROMATIC COMPOUNDS

### XIX. THE REACTION OF BENZENE WITH 1-CYCLOHEXYLCYCLOHEXANOL

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Identical products were obtained in the reaction, described in the preceding paper [1], of 4-cyclohexylcyclohexanol with benzene in presence of aluminum chloride and concentrated sulfuric acid: (3-dicyclohexyl) benzene, (4-dicyclohexyl) benzene and a reduction product—dicyclohexyl. The latter, in the case of reaction in presence of sulfuric acid, contained a trace of impurity, apparently phenylcyclohexane or diphenyl.

In continuation of our work in this field, we have studied the reaction of benzene with 1-cyclohexylcyclohexanol in presence of the same catalysts (aluminum chloride and sulfuric acid). We were interested in the possibility of preparation of tert-(1-dicyclohexyl) benzene. Earlier work [2] suggested that its formation might be expected with the aid of sulfuric acid as catalyst. However, the products obtained both with sulfuric acid and aluminum chloride were the same as those formed from 4-cyclohexylcyclohexanol: dicyclohexyl, (3-dicyclohexyl)- and (4-dicyclohexyl) benzenes. (1-Dicyclohexyl) benzene was not formed at all in these reactions.

Reactions in presence of aluminum chloride were performed in the same way as the corresponding reactions with 4-cyclohexylcyclohexanol. Yields of (dicyclohexyl)benzenes were 40-44%. The main product, as before, was (3-dicyclohexyl) benzene, but in the present case its content in the mixture of isomers was slightly higher. In the majority of experiments the resulting mixture of (dicyclohexyl) benzenes did not crystallize on standing and cooling. Only in two cases did crystals of (4-dicyclohexyl) benzene separate after redistillation of the product from the last fractions. The yield of dicyclohexyl varied considerably in different experiments even under very similar conditions. It was 11.5 to 26% of theory.

In the reactions in presence of sulfuric acid the yields of dicyclohexyl and (dicyclohexyl) benzenes varied widely in dependence on the conditions, although the total yield only altered slightly. With decrease in quantity of sulfuric acid and with falling temperature, the yields of dicyclohexyl increased just as in the reaction with 4-cyclohexylcyclohexanol.

In the course of identification of the substances obtained from 1-cyclohexylcyclohexanol it was particularly important not to overlook the possibility of the presence of tert-(1-dicyclohexyl) benzene. Hydrogenation and dehydrogenation reactions were applied to this end. Dehydrogenation of the products of alkylation took place easily and smoothly with formation only of m- and p-terphenyls. The facility of the reaction and the absence from the products of dehydrogenation of diphenyl and o-terphenyl (or triphenylene) indicates the absence of (1-dicyclohexyl) benzene from the initial product. Even more conclusive proof of the presence of (3-dicyclohexyl)- and (4-dicyclohexyl) benzenes was obtained by hydrogenation to the known 1, 3- and 1, 4-dicyclohexylcyclohexanes and by the preparation of crystalline acet- and benzamino derivatives of (3-dicyclohexyl) benzene. The latter were identical with the corresponding derivatives obtained in the preceding investigation [1].

In these reactions there is consequently no difference between the catalytic activity of sulfuric acid and that of aluminum chloride, as was observed in the alkylation of methylcyclohexenes [2]: neither aluminum chloride nor sulfuric acid gives a tertiary alkylate. The behavior of cyclohexylcyclohexanols in alkylation reactions is reminiscent of that of phenylcyclohexanol and of substances (capable of forming the latter during the reaction) from which with benzene and aluminum chloride only 1,3- and 1,4-diphenylcyclohexanes and phenylcyclohexane are obtained under any desired conditions [3, 4].

## EXPERIMENTAL

**Chlorocyclohexane.** A mixture of 200 g of cyclohexanol, 600 ml of fuming hydrochloric acid and 100 g of anhydrous calcium chloride was refluxed in a flask for 5 hr at 70–80°. The resulting organic layer was separated, washed with cold, concentrated sulfuric acid, then several times with water, dried over calcium chloride, and distilled. B. p. 138–140° (720 mm). Yield 90%.

**1-Cyclohexylcyclohexanol** [5]. Prepared by Grignard reaction from chlorocyclohexane and cyclohexanone. The product was twice distilled in vacuo. B. p. 134–137° (13 mm), m. p. 53–55°. Yield 40%. Literature data [5]: b. p. 135–136° (15 mm), m. p. 53–54°.

### Alkylation of Benzene with 1-Cyclohexylcyclohexanol in Presence of Aluminum Chloride

The reaction was performed as described in the preceding paper. Results of the most typical experiments are set forth in Table I.

The dicyclohexyl fraction came over at 109–110° (13 mm). It had the following constants after further purification with concentrated sulfuric acid:

B. p. 133–35° (40 mm),  $n_D^{20}$  1.4798,  $d_4^{20}$  0.8850,  $MR_D$  53.36. Calculated 53.22.

The fraction of (dicyclohexyl) benzenes distilled at 155–166° (3 mm). Redistillation over sodium gave a product with the constants:

B. p. 145–148° (1.5 mm),  $n_D^{20}$  1.5351,  $d_4^{20}$  0.9738,  $MR_D$  77.50. Calculated 77.32.

Found %: C 88.94, 89.48; H 11.08, 10.55.  $C_{18}H_{26}$ . Calculated %: C 89.19; H 10.81.

After dilution with an equal volume of absolute ether and cooling to –80°, the product turned cloudy but did not crystallize. Only the products of the two following experiments ( $n_D^{20}$  1.5323–1.5337) partly crystallized on standing. The crystals were identified as (4-dicyclohexyl) benzene with m. p. 84° (from alcohol).

TABLE 1

Alkylation of Benzene with 1-Cyclohexylcyclohexanol in Presence of Aluminum Chloride

Molar ratio $C_6H_{11}C_6H_{10}OH$ : $AlCl_3:C_6H_6$	Reaction conditions			Yield, %		
	standing at 15–20° (days)	heating (hr)	tempera- ture	dicyclo- hexyl	(dicyclo- hexyl) benzenes	disubstituted products
1:1:70	1	17	40–75°	23.0	40.0	11.8
1:1:100	3	15	40–80	26.6	33.8	
1:1:40	1	6	40–80	11.5	39.4	6.3
1:1:49	1	15	40–70	14.0	44.3	5.0
1:1.06:45	3	7	60–85	12.9	41.2	13.6

Nitration of 1.2 g of the fraction with 6 ml of nitrating mixture at room temperature for 10 min gave 1.3 g (91%) of a mixture of nitro compounds distilling at 180–200°C (2–3 mm). This was reduced with tin and hydrochloric acid and the resulting amine acetylated and benzoyleated. The following were isolated: p-(4-dicyclohexyl) benzanilide with m.p. 249–250°C (from a mixture of alcohol and benzene), p-(3-dicyclohexyl) benzanilide with m.p. 174–175° (from alcohol) and p-(3-dicyclohexyl) acetanilide with m.p. 165–166°C (from alcohol). None of these derivatives caused a depression of melting point when mixed with the corresponding derivatives prepared in the preceding investigation.

Heating of the mixture of (dicyclohexyl) benzenes with 20% platinized carbon led to vigorous evolution of hydrogen which soon ceased. The mixture was boiled for another hour. The product was extracted with benzene, and the following were isolated by crystallization: p-terphenyl with m. p. 208–210° (from a mixture of alcohol and benzene) and m-terphenyl with m. p. 86° (from alcohol).

Hydrogenation of (dicyclohexyl) benzenes in alcoholic solution over Raney nickel at 160-180° and at 80 atm hydrogen pressure gave a mixture of dicyclohexylcyclohexanes from which, by crystallization from alcohol from a mixture of alcohol and benzene and from acetone, was isolated the solid stereoisomer of 1,3-dicyclohexylcyclohexane in the form of needles with m. p. 62-64° (from a mixture of alcohol and benzene), also a small quantity of trans-1,4-dicyclohexylcyclohexane in the form of leaflets with m. p. 163-164.5° (from alcohol or acetone). They were identified by the melting points of mixtures with the specimens described in the preceding investigation. A large part of the hydrogenation product remained liquid and consisted mainly of 1,3-dicyclohexylcyclohexane.

#### Alkylation of Benzene with 1-Cyclohexylcyclohexanol in Presence of Sulfuric Acid

The reaction was carried out in the manner described in the preceding paper. Results of the condensation are set forth in Table 2.

TABLE 2  
Alkylation of Benzene with 1-Cyclohexylcyclohexanol in Presence of Sulfuric Acid

Molar ratio $C_6H_{11}C_6H_{10}OH:$ $H_2SO_4 : C_6H_6$	Reaction conditions		Yield, %	
	tempera- ture	duration, hr	dicyclo- hexyl	(dicyclo- hexyl) benzenes
1 : 3.7 : 35	-2°	5	21.7	16.5
1 : 3.7 : 35	0	5	28.9	16.5
1 : 3.7 : 35	6	5	24.0	11.5
1 : 7.5 : 35	-4	4.5	14.4	17.3
1 : 7.5 : 35	-4	3	21.7	19.8
1 : 15 : 35	0	5	19.8	34.5
1 : 15 : 35	6	5	9.5	38.1
1 : 15 : 35	16-18	5	9.5	50.4

The combined dicyclohexyl fractions (b. p. 80-85° at 2 mm) were repeatedly washed with concentrated sulfuric acid, then with water, dried over calcium chloride, and again distilled over sodium:

B. p. 127° (27 mm),  $n_D^{20}$  1.4802,  $d_4^{20}$  0.8854,  $MR_D$  53.37. Calculated 53.22.

The fractions of dicyclohexylbenzenes were likewise combined and further purified with concentrated sulfuric acid. Distillation over sodium gave a mixture of (3-dicyclohexyl)- and (4-dicyclohexyl) benzenes:

B. p. 152-154° (2 mm),  $n_D^{20}$  1.5340,  $d_4^{20}$  0.9729,  $MR_D$  77.43. Calculated 77.32.

Mixtures of acetyl amino and benzoyl amino derivatives were prepared in the usual manner. From these, by crystallization from alcohol, were isolated p-(3-dicyclohexyl) acetanilide with m. p. 165-166° and p-(3-dicyclohexyl) benzanilide with m. p. 174-175°. These were identical with previously prepared specimens.

Dehydrogenation of the fraction by heating with platinized carbon at 300-320° was completed in 20-30 min and gave a mixture of m-, p-terphenyls in 90% yield, of which 80-85% consisted of the meta-isomer.

#### SUMMARY

The reaction of benzene with 1-cyclohexylcyclohexanol in presence of aluminum chloride or sulfuric acid gave products identical with those obtained in the corresponding reactions with 4-cyclohexylcyclohexanol: dicyclohexyl and (3-dicyclohexyl)- and (4-dicyclohexyl) benzenes.

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# INVESTIGATION OF THE EXCHANGE BETWEEN TERTIARY ALCOHOLS AND THE CORRESPONDING HYDROCARBONS IN PRESENCE OF SULFURIC ACID

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In the recent literature the hypothesis of carbonium ion formation in certain reactions has been used. It has been shown, for example, in [1] that the mechanism of alkylation with alcohols in presence of  $\text{BF}_3$  involves formation of a carbonium ion which subsequently reacts with the aromatic ring.

In one of our papers [2] we investigated the radical exchange between aromatic hydrocarbons and their halogenated derivatives in presence of  $\text{AlCl}_3$ . It was suggested that exchange proceeds through intermediate formation of carbonium ions.

Extensive investigations by D. N. Kursanov and co-workers [3, 4] also demonstrated the participation of hydrocarbon carbonium ions in the hydrogen exchange of tertiary alcohols during reaction with deuterioacids. The authors noted that primary and secondary alcohols do not exchange their hydrogen for deuterium and that exchange of the aliphatic radical in tertiary alcohols with an aromatic radical greatly inhibits the hydrogen exchange reaction. The authors explained this effect in terms of a delocalization of the positive charge of the carbonium ion when the tertiary carbon is linked to an aromatic radical.

If carbonium ions are formed in the reaction of tertiary alcohols with acids, we reasoned that it should be possible to investigate carbocationic exchange between  $\text{C}^{14}$ -labeled tertiary alcohols and the corresponding tertiary hydrocarbons in presence of concentrated sulfuric acid. For this purpose we synthesized a number of  $\text{C}^{14}$ -labeled tertiary alcohols: dimethylethylcarbinol, dimethylphenylcarbinol, 1-methylcyclohexanol-1 and 1-phenylcyclohexanol-1.

The reaction was carried out at room temperature with agitation on a shaking machine. The alcohol/hydrocarbon/sulfuric acid molar ratio was 1:1:3. After the reaction the tertiary hydrocarbon was isolated and analyzed for its content of radiocarbon. Experimental results are set forth in the table.

We see from the table that carbocationic exchange, like the previously noted hydrogen exchange [3,4], is only observed in tertiary alcohols. Phenol (expt. 6) does not manifest exchange activity with a hydrocarbon in presence of sulfuric acid.

These data are consequently in good accord with the results obtained by D. N. Kursanov and co-workers for hydrogen exchange of alcohols during interaction with acids.

The experiments showed that aliphatic and aromatic substituents exert the same influence as in the case of H-D exchange of alcohols with acids. Comparison of results obtained in experiments with dimethylethylcarbinol and dimethylphenylcarbinol, and also with 1-methylcyclohexanol-1 and 1-phenylcyclohexanol-1 carried out under identical conditions, indicates that exchange of the ethyl or methyl radical with the phenyl radical markedly slows down the rate of exchange (expts. 1, 2 and 3, 5).

## EXPERIMENTAL

Exchange reactions of labeled tertiary carbinol with the corresponding hydrocarbons were carried out with shaking on a machine at room temperature in presence of sulfuric acid.

To a mixture of 0.02 mole of labeled carbinol and 0.02 mole of hydrocarbon in a 50 ml bottle (fitted with a ground stopper) was added dropwise a triple excess of concentrated sulfuric acid. After shaking for a determined

period, the reaction mixture was decomposed with water, and the organic layer was separated from the aqueous layer, washed free of sulfuric acid, and dried with potassium carbonate. To the tertiary hydrocarbon, distilled off in vacuo, were added a few small pieces of metallic sodium, and the product was redistilled in vacuo.

Investigation of the Exchange Between Tertiary Alcohols and the Corresponding Hydrocarbons in Presence of Sulfuric Acid

Expt. No.	Exchanging system	Period of contact (hr)	Temperature	Initial radioactivity of the alcohol (pul./min)	Radioactivity found in hydrocarbon after exchange (pul./min)	% of exchange	Initial radioactivity of halogenated derivative taken for synthesis of the carbinol by Grignard reaction
1	$\begin{array}{c} \text{C}_6\text{H}_5 \\   \\ \text{H}_3\text{C}-\text{C}-\text{OH} + \text{H}_3\text{C}-\text{C}-\text{H} \\   \quad \quad   \\ \text{CH}_3 \quad \quad \text{CH}_3 \end{array}$	30	18°	1250	70	5.6	$\text{C}_6^{14}\text{H}_5\text{Br}$
2	$\begin{array}{c} \text{C}_2\text{H}_5 \\   \\ \text{H}_3\text{C}-\text{C}-\text{OH} + \text{H}_3\text{C}-\text{C}-\text{H} \\   \quad \quad   \\ \text{CH}_3 \quad \quad \text{CH}_3 \end{array}$	30	18	1841	355	20.0	$\text{C}_2^{14}\text{H}_5\text{I}$
3	$\begin{array}{c} \text{C}_6\text{H}_5 \\   \\ \text{C}-\text{OH} \\   \\ \text{H}_3\text{C}-\text{C}-\text{CH}_3 \\   \quad   \\ \text{H}_3\text{C} \quad \text{CH}_3 \end{array} + \begin{array}{c} \text{C}_6\text{H}_5 \\   \\ \text{C}-\text{H} \\   \\ \text{H}_3\text{C}-\text{C}-\text{CH}_3 \\   \quad   \\ \text{H}_3\text{C} \quad \text{CH}_3 \end{array}$	15	18	835	220	26.6	$\text{C}_6^{14}\text{H}_5\text{Br}$
4	$\begin{array}{c} \text{C}_6\text{H}_5 \\   \\ \text{C}-\text{OH} \\   \\ \text{H}_3\text{C}-\text{C}-\text{CH}_3 \\   \quad   \\ \text{H}_3\text{C} \quad \text{CH}_3 \end{array} + \begin{array}{c} \text{C}_6\text{H}_5 \\   \\ \text{C}-\text{H} \\   \\ \text{H}_3\text{C}-\text{C}-\text{CH}_3 \\   \quad   \\ \text{H}_3\text{C} \quad \text{CH}_3 \end{array}$	60	18	835	334	40.0	
5	$\begin{array}{c} \text{C}_6\text{H}_5 \\   \\ \text{C}-\text{OH} \\   \\ \text{H}_3\text{C}-\text{C}-\text{CH}_3 \\   \quad   \\ \text{H}_3\text{C} \quad \text{CH}_3 \end{array} + \begin{array}{c} \text{C}_6\text{H}_5 \\   \\ \text{C}-\text{H} \\   \\ \text{H}_3\text{C}-\text{C}-\text{CH}_3 \\   \quad   \\ \text{H}_3\text{C} \quad \text{CH}_3 \end{array}$	15	18	1830	647	35.3	$\text{C}_6^{14}\text{H}_5\text{I}$
6*	$\text{C}_6^{14}\text{H}_6 + \text{C}_6\text{H}_5\text{OH}$	10	18	3500	0	0	—
7*		10	70	3500	8	0.2	—

\* In expts. 6 and 7 the initial radioactivity relates to  $\text{C}_6^{14}\text{H}_6$ ; the radioactivity found relates to  $\text{C}_6\text{H}_5\text{OH}$ .

A blank experiment was run for each system with the objective of checking the purity of the isolated product. For this purpose the hydrocarbon was mixed with the labeled alcohol and fractionated under the same conditions. Its activity did not exceed 1% of that of the initial radioactive alcohol. The radiocarbon content of the investigated substances was determined by combustion to  $\text{CO}_2$ , whose activity was measured with an internally filled counter.

#### SUMMARY

1. It was shown that carbocationic exchange takes place at the normal temperature between  $\text{C}^{14}$ -labeled tertiary alcohols and their corresponding hydrocarbons in presence of sulfuric acid.
2. It was found that replacement of the aliphatic radical in the tertiary alcohols by an aromatic radical markedly slows down the rate of exchange.

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## INVESTIGATIONS ON CONJUGATED SYSTEMS

### CXLL DIENIC SYNTHESSES WITH PARTICIPATION

#### OF 2-CHLOROMETHYL-1, 3-BUTADIENE\*

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Numerous investigations have been devoted in the past 15 years to the study of dienic syntheses with participation of halodienes. Little work has been done, however, on reactions of halodienes containing a halogen atom in the allyl position to the conjugated system. The literature merely refers to interaction of some substances with maleic anhydride [1-3]. At the same time the dienic synthesis with participation of allylic halodienes opens out new routes to the preparation of derivatives of cyclohexene and cyclohexadiene due to transformations of the halogen atom of the adducts.

The objective of the present work was the study of dienic condensation reactions of a halodiene of the type in question—2-chloromethyl-1, 3-butadiene—with mono- and dibasic acids and their derivatives (methyl acrylate and acrylonitrile, methacrylic acid and its methyl ester, propiolic acid and its methyl ester, and the dimethyl esters of fumaric and acetylenedicarboxylic acids).

Condensation was carried out in sealed glass tubes at 140-160°. Hydrogen chloride was usually evolved when the tubes were opened—evidence of partial dehydrochlorination of the reaction products. Dehydrochlorination was likewise observed earlier in the condensation of halodienes with maleic anhydride [1-3]. Splitting out of hydrogen halide from the adducts leads to a new conjugated system which in turn can condense with maleic anhydride. The product of condensation of 2-chloromethyl-1, 3-butadiene with maleic anhydride, for example, contained only traces of chlorine and consisted of the anhydride of the corresponding tetracarboxylic acid [3].

In all cases we obtained chlorine-containing adducts, although their yields were small (30-40%) and the chlorine content was sometimes somewhat below the theoretical value.

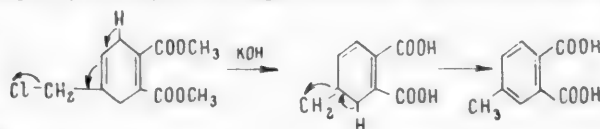
Isolation of the condensation products was further complicated by the partial conversion of 2-chloromethyl-1, 3-butadiene during heating to a dimer which could not always be easily separated from the products of the dienic synthesis. These two factors prevented us in a number of cases from isolating the adducts in a sufficiently pure state.

Adducts with unsymmetrical dienophiles are apparently mixtures of meta- and para-isomers [4, 5]. *m*-Toluylic acid, for example, was isolated from the products of hydrolysis of the adduct of propiolic acid.

A characteristic feature of all the prepared condensation products was the high mobility of the chlorine atom. Mixing of alcoholic solutions of the adducts with alcoholic NaOH, for example, led to considerable heat development with quantitative separation of sodium chloride.

A similar type of transformations of dienic adducts containing an allylic halogen atom has been mentioned in the literature. Hydrolysis of the product of condensation of 1, 6-dibromo-2, 4-hexadiene with maleic anhydride gave a double lactone [6].

We obtained 4-methylphthalic acid (described in the literature) by treatment with alcoholic alkali of the dimethyl ester of chloromethylcyclohexadienedicarboxylic acid formed on condensation of 2-chloromethyl-1, 3-butadiene with dimethyl acetylenedicarboxylate. 5-Methylene-1, 3-cyclohexadienecarboxylic acid, probably formed as an intermediate, easily undergoes prototropic rearrangement in an alkaline medium with formation of an aromatic ring.



\* Dienic compounds, LXXXXI.

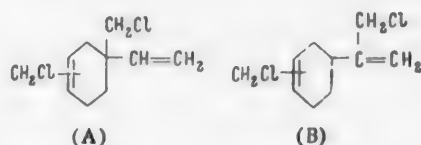


Fractional distillation of the condensation products nearly always gave us fractions containing the dimer of chloromethylbutadiene. With the aim of isolating this dimer we subjected chloromethylbutadiene to heating at 140-150° in toluene solution in presence of hydroquinone. Fractionation of the reaction mixture gave two fractions of reaction products and a residue which distilled with decomposition.

The lower boiling fraction contained a considerably higher percentage of chlorine than was present in the initial substance; it was most probably a mixture of addition products of hydrogen chloride and 2-chloromethyl-1, 3-butadiene, toluene and dimer.

The higher boiling fraction came over in a narrow temperature range and the analysis indicated that it was the dimer of the original substance.

Depending upon which of the double bonds is the stronger dienophile, the dimer of 2-chloromethyl-1, 3-butadiene could have structure A or B:



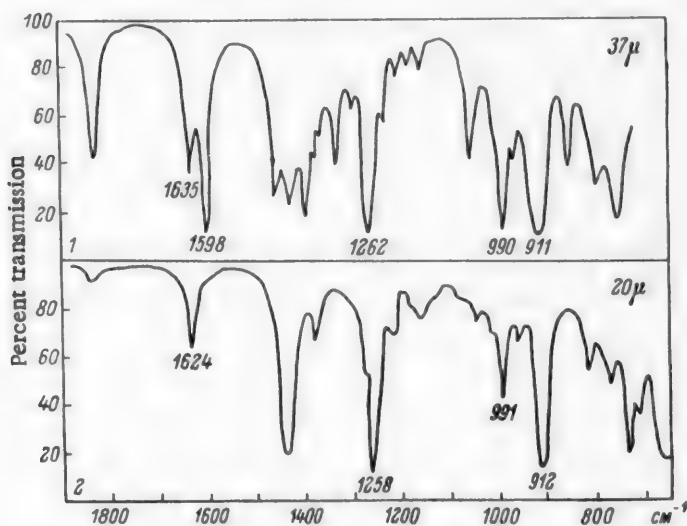
Products of type B predominate considerably in the mixture of dimers from isoprene [7]. Also, chloromethylbutadiene gives dimers exclusively or nearly exclusively of type A.

The infrared spectrum of the dimer, like that of the monomer, contains strong vinyl group frequencies (912, 991 and 1630  $\text{cm}^{-1}$ ), as well as the frequency of the quaternary grouping (1258  $\text{cm}^{-1}$ ), while the band characteristic of the terminal methylene group (890  $\text{cm}^{-1}$ ) is substantially absent. This particular spectrum is compatible only with structures of type A (figure).

Introduction of chlorine into the methyl group evidently weakens its electron-donating properties, and the adjacent double bond becomes more nucleophilic and consequently more dienophilic than the vinyl group.

We did not establish the position (meta or para) of the chloromethyl group in the ring.

Our investigation accordingly established that 2-chloromethyl-1, 3-butadiene normally enters into dienic synthesis reaction with the most diverse dienophiles, although the reaction is complicated by processes of dehalogenation of the adducts and of dimerization of the initial substance.



Infrared transmission spectra. 1) 2-Chloromethyl-1,3-butadiene; 2) its dimer [predominantly 1,4 (or 1,3)-dichloromethyl-1-vinylcyclohexene-3].

## EXPERIMENTAL

2-Chloromethyl-1, 3-butadiene (chloroisoprene) was prepared by chlorination of isoprene [3]. A product with the following constants (agreeing with the literature data) was used in the work.

B. p. 49-51°,  $n_D^{20}$  1.4780-1.4794.

Infrared spectrum: 750 strong, 798 medium, 851 medium, 911 very strong, 990 strong, 1052 medium, 1262 strong, 1328 medium, 1398 strong, 1423 strong, 1453 strong, 1598 strong, 1635 strong, 1828 strong  $\text{cm}^{-1}$ .

Condensation with methyl acrylate. A mixture of 10.3 g of chloroisoprene, 13.9 g of methyl acrylate and 10 g of toluene (+ hydroquinone) was heated at 130-140° for 10 hr. There was obtained 7.6 g of condensation product with b. p. 123-125° (10 mm). A second fractionation gave sufficiently pure methyl ester of 3 (or 4)-chloromethylcyclohexene-3-carboxylic acid.

B. p. 124-125° (10 mm),  $d_4^{20}$  1.1480,  $n_D^{20}$  1.4936, MR 47.82. Calculated 47.61.

Found %: Cl 18.63;  $\text{OCH}_3$  16.17.  $\text{C}_9\text{H}_{13}\text{O}_2\text{Cl}$ . Calculated %: Cl 18.80;  $\text{OCH}_3$  16.43.

Condensation with acrylonitrile. A mixture of 7.2 g of chloroisoprene, 3.7 g of acrylonitrile and 10 g of toluene (+ hydroquinone) was heated at 140-150° for 12 hr. Hydrogen chloride escaped when the tube was opened. There was obtained 4.2 g (54%) of condensation product with b. p. 125-135° (6 mm). A second fractionation gave 3 (or 4)-chloromethylcyclohexene-3-carboxy nitrile of adequate purity in the form of a colorless, oily liquid which irritated the skin.

B. p. 135-137° (10 mm),  $d_4^{20}$  1.1170,  $n_D^{20}$  1.5062, MR 41.43. Calculated 41.16.

Found %: N 8.83, Cl 23.26.  $\text{C}_8\text{H}_{10}\text{NCl}$ . Calculated %: N 9.00; Cl 22.75.

Condensation with methacrylic acid and its methyl ester. a) A mixture of 5.1 g of chloroisoprene, 4.3 g of methacrylic acid and 5 ml of toluene (+ hydroquinone) was heated at 120-130° for 12 hr. There was obtained 1-methyl-3(4)-chloromethylcyclohexene-3-carboxylic acid with the following constants:

B. p. 133-136° (20 mm),  $d_4^{20}$  1.1580,  $n_D^{20}$  1.4901, MR 46.83. Calculated 46.40.

Found %: Cl 18.37. Acid equiv. 192.1.  $\text{C}_9\text{H}_{13}\text{O}_2\text{Cl}$ . Calculated %: Cl 18.79 Acid equiv. 188.7.

b) A mixture of 12 g of methyl methacrylate, 10.2 g of chloroisoprene and 10 ml of toluene (+ hydroquinone) was heated at 150-160° for 14 hr. A considerable quantity of hydrogen chloride was evolved when the tube was opened.

Fractionation of the reaction products gave the following fractions: (10 mm): 1st, 120-125°, 1.7 g; 2nd, 125-127°, 9.6 g; 3rd, 127-140°, 2.1 g.

The following constants were found for the second fraction (contaminated with the dimer of methyl 1-methyl-3(4)-chloromethylcyclohexene-3-carboxylate:

$d_4^{20}$  1.1090,  $n_D^{20}$  1.4920, MR 53.01. Calculated 52.44.

Found %: Cl 18.68;  $\text{OCH}_3$  14.13.  $\text{C}_{10}\text{H}_{15}\text{O}_2\text{Cl}$ . Calculated %: Cl 17.49;  $\text{OCH}_3$  15.67.

Condensation with propiolic acid and its methyl ester. a) A mixture of 4.5 g of chloroisoprene, 3.1 g of propiolic acid and 5 ml of toluene (+ hydroquinone) was heated at 130° for 12 hr. Hydrogen chloride was evolved when the tube was opened. The condensation product came out of solution as a precipitate. After filtration, washing with toluene, and drying, it weighed 3.1 g (40%).

The substance was purified by chromatography on alumina. The chloromethylcyclohexadiene-1, 4-carboxylic acid, separated from the upper part of the column, had m. p. 166-168°.

Found %: Cl 20.04. Acid equiv. 173.4.  $\text{C}_8\text{H}_9\text{O}_2\text{Cl}$ . Calculated %: Cl 20.54. Acid equiv. 172.6.

From the lower part of the column was isolated a small quantity of substance with m. p. 147-150°. It was not further examined.

b) A mixture of 1.95 g of methyl propiolate, 2.5 g of chloroisoprene and 5 ml of toluene (+ hydroquinone) was heated at 140° for 12 hr. There was obtained 1.3 g (45%) of methyl 3-(4)-chloromethylcyclohexadiene-1,4-carboxylate contaminated with dimer.

B. p. 137-139° (10 mm),  $d_4^{20}$  1.1650,  $n_D^{20}$  1.5208, MR 48.7. Calculated 47.15.

Found %: Cl 19.80; OCH<sub>3</sub> 13.68. C<sub>9</sub>H<sub>11</sub>O<sub>2</sub>Cl. Calculated %: Cl 19.00; OCH<sub>3</sub> 16.63.

Condensation with dimethyl fumarate. A mixture of 4.6 g of chloroisoprene, 6.2 g of dimethyl fumarate and 7 ml of toluene (+ hydroquinone) was heated at 130-140° for 12 hours. There was obtained 4.1 g of condensation product (39%) with b. p. 168-173° (10 mm). Redistillation gave dimethyl 4-chloromethylcyclohexene-4-dicarboxylate of adequate purity.

B. p. 170-173° (10 mm),  $d_4^{20}$  1.2090,  $n_D^{20}$  1.4916, MR 59.17. Calculated 58.51.

Found %: Cl 14.15; OCH<sub>3</sub> 24.96. C<sub>11</sub>H<sub>15</sub>O<sub>4</sub>Cl. Calculated %: Cl 14.37; OCH<sub>3</sub> 25.15.

Condensation with dimethyl acetylenedicarboxylate. A mixture of 6.5 g of chloroisoprene, 8.0 g of ester and 10 ml of toluene (+ hydroquinone) was heated at 145° for 10 hr. A considerable quantity of hydrogen chloride was detected when the tube was opened. Fractional distillation in vacuo (10 mm) gave 9.8 g (67%) of condensation product. Redistillation gave not perfectly pure dimethyl 4-chloromethylcyclohexadiene-1, 4-dicarboxylate.

B. p. 187-190° (10 mm),  $d_4^{20}$  1.2422,  $n_D^{20}$  1.5144, MR 59.38. Calculated 58.04.

Found %: Cl 11.39; OCH<sub>3</sub> 25.43. C<sub>11</sub>H<sub>13</sub>O<sub>4</sub>Cl. Calculated %: 14.49; OCH<sub>3</sub> 25.37.

To 2.4 g of the ester was added 20 ml of 10% alcoholic sodium hydroxide. A violent reaction at once commenced with separation of sodium chloride and release of heat. After refluxing for 4 hr, the alcohol was taken off in vacuo, the residue dissolved in 15 ml of water, and the solution acidified with sulfuric acid and extracted with ether. Removal of the ether left 1.2 g (67%) of crystalline product with m. p. 134-140°. Recrystallization of the substance from benzene and acetone gave pure 4-methylphthalic acid with m. p. 151-152° (with rapid heating).

Found %: C 60.15; H 4.16. Acid equiv. 90.97. C<sub>9</sub>H<sub>8</sub>O<sub>4</sub>. Calculated %: C 60.00; H 4.42. Acid equiv. 90.08.

The whole of the chlorine originally contained in the sample of ester was found in the initial alkaline solution in the form of chloride ion.

Dimerization of 2-chloromethyl-1, 3-butadiene. A mixture of 23 g of chloroisoprene and 12 ml of toluene (+ hydroquinone) was heated at 140-150° for 12 hr. Fractional distillation of the reaction mixture in vacuo gave two liquid products and a resinified residue (5.8 g).

1st fraction (3.2 g). B. p. 56-61° (10 mm),  $n_D^{20}$  1.4850.

Found %: C 49.69, 49.77; H 6.50, 6.56; Cl 45.20, 45.16.

2nd fraction (6.6 g of dimer). B. p. 129-131° (10 mm),  $d_4^{20}$  1.1360,  $n_D^{20}$  1.5240, MR 55.24. Calculated 54.98.

Found %: C 58.84, 58.81; H 7.06, 7.09; Cl 35.31, 35.37. C<sub>10</sub>H<sub>14</sub>Cl<sub>2</sub>. Calculated %: C 58.54, H 6.88; Cl 34.56.

Infrared spectrum: 670 strong, 740 strong, 912 strong, 991 medium, 1258 strong, 1432 strong, 1630 medium, 1842 weak cm<sup>-1</sup>.

#### SUMMARY

1. 2-Chloromethyl-1, 3-butadiene was condensed with the methyl esters of acrylic, methacrylic, fumaric, propiolic and acetylenedicarboxylic acids, with methacrylic and propiolic acids, and with acrylonitrile.

2. It was shown that in all cases the condensation is accompanied by processes of dehydrohalogenation of the adducts and dimerization and polymerization of the chloroisoprene.

3. The expected condensation products were isolated in adequate purity and were characterized: methyl esters of 3 (4)-chloromethylcyclohexene-3-carboxylic acid, 3(4)-chloromethylcyclohexadiene-1, 4-carboxylic acid, 4-chloromethylcyclohexene-4-dicarboxylic acid, the nitrile of 3 (4)-chloromethylcyclohexene-3-carboxylic acid and 3 (4)-chloromethylcyclohexene-3-carboxylic acid. In the remaining cases adducts were obtained whose halogen content was less than the theoretical requirement.

4. It was established that the chlorine atom in all of the adducts is extremely mobile and is easily split off during separation of the substances or by the action of caustic alkalis. 4-Methylphthalic acid was obtained from the product of condensation of chloroisoprene with dimethyl acetylenedicarboxylate by treatment with alkali.

5. It was shown that heating of chloromethylbutadiene causes the latter to dimerize to predominantly 1,4 (1,3)-dichloromethyl-1-vinylcyclohexene-3.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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## STUDIES OF THE CHEMISTRY OF ORGANIC OXIDES

### XXL THE COMBINATION OF PHENOLS WITH DIVINYLCYCLOHEXADIENE

#### AND ISOPRENE OXIDES

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Alcohols combine with unsymmetrical saturated  $\alpha$ -oxides in the presence of alkaline catalysts in accordance with the rule of A. K. Krasuskii, which he established for reactions with amines. Unsaturated  $\alpha$ -oxides likewise react with alcohols under the same conditions; however, in this case the amount of isomeric addition products (not formed in accordance with Krasuskii's rule) may be as much as 30-35% [1,2].

Phenol combines with propylene oxide in an alkaline medium with the formation of a primary ether of propylene glycol [3,4], while styrene oxide yields a mixture of the two possible ethers, the ratio between them depending on the reaction conditions; the quantity of the primary alcohol in some cases reaches as high as 80% [5-7].

The reactions of diene oxides with phenols have not been studied.

We have determined, as a result of experiments that we have carried out, that phenols combine with divinyl, chloroprene and isoprene oxides in an alkaline medium to give a yield that consists preponderantly of the primary ethers of the corresponding glycols. The content of the latter in the reaction products varies, in the case of phenol and its halogen derivatives, within the limits 65-90%. The experimental data are shown in Table 1.

From the data in Table 1 it can be seen that the ratios between the quantities of the isomeric ethers for the oxides of divinyl and isoprene are close to each other (1:4). Chloroprene oxide combines with phenol with the formation of a considerably larger quantity of the secondary ether than does divinyl oxide. An analogous phenomenon was previously observed in the case of the addition of alcohols to these oxides [2]. Meanwhile, if the vicinal effect of the chlorine atom [8] is taken into consideration, one would expect the reverse ratio. It is possible that the decisive factor, which in this case determines the order of addition, is the increase in positive polarization under the influence of the  $C_2$  halogen atom, as a result of which it is able to compete with the  $C_1$  atom in nucleophilic attack on an alkoxy or phenoxy ion.

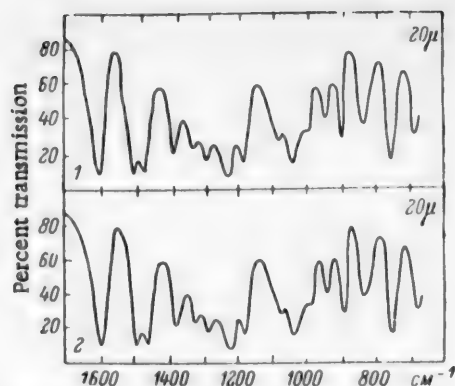
p-Chlorophenol combines with chloroprene oxide with the formation of a larger quantity of secondary ether than in the case of unsubstituted phenol. This is apparently due to the more acid character of p-chlorophenol.

The opposite picture is observed in the case of o-chlorophenol. It is possible the spatial difficulties hinder the entrance of an o-chlorophenoxy ion into the second position.

The structure of the addition products of phenols with unsaturated oxides was determined by several methods. First, the amount of primary alcohols in these addition products was determined by the phthalic anhydride method. Second, these addition products were hydrogenated and the content of primary alcohols determined in the mixture of saturated ethers by the same method.

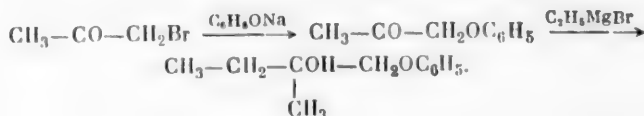
The suitability of the phthalic anhydride method for this purpose was confirmed with artificial mixtures of known isomers of glycol ethers.

Finally, the hydrogenation products of the expected glycol ethers were prepared in a pure state by independent synthesis and their constants and infrared spectra were compared with the corresponding data on the substances obtained from the oxides.



Infrared transmission spectra, 1) 1-Phenoxy-2-methylbutanol-2 prepared by the hydrogenation of the addition product of phenol and isoprene oxide; 2) the same product prepared from phenoxyacetone.

In order to identify the principal addition product of phenol with isoprene oxide, the corresponding saturated ether was prepared as follows:



The constants and infrared spectrum of this compound (see figure and Table 2) coincided with the corresponding data for the hydrogenated product of the compound formed by the reaction of phenol with isoprene oxide.

#### EXPERIMENTAL

The unsaturated oxides were prepared by the distillation of halogen hydrins over alkali (chlorohydrins in the case of divinyl and isoprene oxides and bromohydrin in the case of chloroprene oxide) [8-10].

The reaction of the oxides with phenol was carried out under the following conditions. Phenol (0.05 g-mole) and 0.3 g of sodium were dissolved in 50 ml of anhydrous dioxane, after which 0.05 g-mole of oxide were added to the solution. The reaction mixture was heated for a certain time with a reflux condenser until boiling occurred; then the dioxane was distilled off and the remainder distilled in vacuo. The constants and analytical data for these products are shown in Table 1.

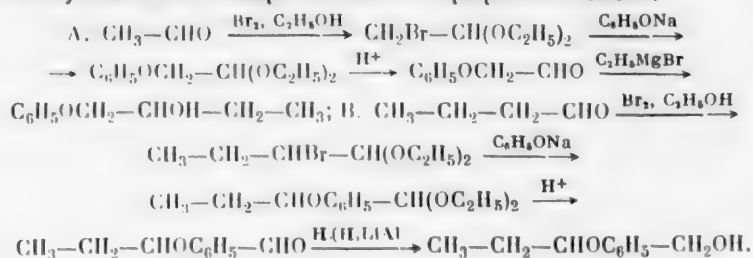
Hydrogenation of these phenoxyalcohols (about 0.01 g-mole) was carried out in methyl alcohol (25 ml) over Pd/CaCO<sub>3</sub> (about 1 g with a content of about 1 mg of Pd) until the absorption of hydrogen ceased, which usually required from three to five hours.

In order to check the suitability of the phthalic anhydride method for this case, a mixture of 1.3079 g of 1-phenoxybutanol-2 and 0.4275 g of 2-phenoxybutanol-1 was prepared. Primary alcohol, 25.4% (calculated 24.6%), was found in this mixture by the well-known procedure [11].

**1-Phenoxybutanol-2.** An ether solution of 20 g of phenoxyacetic aldehyde (prepared from acetal) [12, 13] was added drop by drop with vigorous stirring to a chilled solution of ethyl magnesium bromide, prepared from 11.5 g of magnesium. The reaction mixture was left overnight at room temperature and then heated to the boiling point of ether for three hours. It was then decomposed with 10% hydrochloric acid. The ether extract was dried over sodium sulfate. The constants and analytical data for the product obtained are shown in Table 2.

**2-Phenoxybutanol-1.** The acetal of  $\alpha$ -bromobutyric aldehyde [12] was heated with an alcohol solution of sodium phenolate (prepared from 32 g of phenol and 8 g of sodium in 80 ml of anhydrous ethanol) in an autoclave

The isomeric phenyl ethers of  $\alpha$ -butyleneglycol which were needed for the identification of the addition products of phenol with divinyl oxide and chloroprene oxide were prepared as follows:



The constants of these compounds are shown in Table 2. It should be noted that, on comparing the indices of refraction of the pure ethers and their mixture obtained by the hydrogenation of the addition products of phenol and divinyl oxide, the same ratio between the quantities of isomers was found as was found by the phthalic anhydride method.



TABLE 1.

Results of Experiments on the Addition of Phenols to Unsaturated Oxides

Oxide	Phenol	Reaction time, hr	Total yield of add. products, %	Reaction products	Content, %	B. p. (mm)	$d_4^{20}$	$n_D^{20}$	MR		Found, %			Calculated, %		
											found	calc.	red	C	H	Cl
$\text{CH}_2=\text{CH}-\text{CH}-\text{CH}_2$   O	$\text{C}_6\text{H}_5\text{OH}$	18	80	$\text{CH}_2=\text{CH}-\text{CH}(\text{OH})-\text{CH}_2\text{OC}_6\text{H}_5$ $\text{CH}_2=\text{CH}-\text{CH}(\text{OC}_6\text{H}_5)-\text{CH}_2\text{OH}$	80 20	101-102°	1.0721	1.5350	47.70	47.48	73.26, 73.21	—	—	73.14	7.37	—
	$\text{C}_6\text{H}_5\text{OH}$	18	85	$\text{CH}_2=\text{CCl}-\text{CH}(\text{OH})-\text{CH}_2\text{OC}_6\text{H}_5$ $\text{CH}_2=\text{CCl}-\text{CH}(\text{OC}_6\text{H}_5)-\text{CH}_2\text{OH}$	65 35	131-132	1.1961	1.5458	52.58	52.35	60.72, 60.85	17.86, 17.95	—	60.46	5.58	17.85
$\text{CH}_2=\text{CCl}-\text{CH}-\text{CH}_2$   O	$o\text{-C}_6\text{H}_4\text{ClOH}$	36	75	$\text{CH}_2=\text{CCl}-\text{CH}(\text{OH})-\text{CH}_2\text{OC}_6\text{H}_4\text{Cl}$ $\text{CH}_2=\text{CCl}-\text{CH}(\text{OC}_6\text{H}_4\text{Cl})-\text{CH}_2\text{OH}$	90 10	148-149	1.3001	1.5550	57.49	57.21	51.55, 51.74	4.56, 4.61	—	51.53	4.32	30.42
	$p\text{-C}_6\text{H}_4\text{ClOH}$	24	80	$\text{CH}_2=\text{CCl}-\text{CH}(\text{OH})-\text{CH}_2\text{OC}_6\text{H}_4\text{Cl}$ $\text{CH}_2=\text{CCl}-\text{CH}(\text{OC}_6\text{H}_4\text{Cl})-\text{CH}_2\text{OH}$	75 25	168	1.3010	1.5558	57.53	57.21	51.70, 51.62	4.45, 4.57	—	51.53	4.32	30.42
$\text{CH}_3$   $\text{CH}_2=\text{CH}-\text{C}-\text{CH}_2$   O	$\text{C}_6\text{H}_5\text{OH}$	36	70	$\text{CH}_2=\text{CH}-\text{COH}-\text{CH}_2\text{OC}_6\text{H}_5$ $\text{CH}_2=\text{CH}-\text{CO}(\text{C}_6\text{H}_5)-\text{CH}_2\text{OH}$   $\text{CH}_3$	77 23	109-110	-1.0427	1.5238	52.30	52.10	74.08, 74.04	7.89, 7.89	—	74.13	7.92	—
	$\text{C}_6\text{H}_5\text{OH}$	36	70	$\text{CH}_2=\text{CH}-\text{CO}(\text{C}_6\text{H}_5)-\text{CH}_2\text{OH}$   $\text{CH}_3$	23	116-117	1.0546	1.5330	52.45	52.10	74.59, 74.50	7.50, 7.42	—	74.13	7.92	—

TABLE 2.

Constants and Analytical Data for Isomeric Phenyl Glycol Ethers

Compound	B. p. (10 mm)	$d_4^{20}$	$n_D^{20}$	MR		Found, %		Calculated, %		
				found	calc.	C	H	Empirical formula	C	H
$\text{CH}_3-\text{CH}_2-\text{CHOH}-\text{CH}_2\text{OC}_6\text{H}_5$	124° [14]	1.0395	1.5170	48.33	47.95	72.12	72.38	$\text{C}_{10}\text{H}_{14}\text{O}_2$	72.25	8.49
$\text{CH}_3-\text{CH}_2-\text{CHOC}_6\text{H}_5-\text{CH}_2\text{OH}$	125-126	1.0425	1.5214	48.43	47.95	72.74	72.76	$\text{C}_{10}\text{H}_{14}\text{O}_2$	72.25	8.49
Hydrogenation products obtained from phenol and diethyl oxide addition products (H <sub>2</sub> absorbed, 97.3% of theoretical)	124	1.0403	1.5181	48.48	47.95	72.49	72.43	$\text{C}_{10}\text{H}_{14}\text{O}_2$	72.25	8.49
Hydrogenation products of phenol and chloroprene oxide addition products (94% H <sub>2</sub> absorbed)	124	1.0416	1.5188	48.27	48.95	72.57	72.74	$\text{C}_{10}\text{H}_{14}\text{O}_2$	72.25	8.49
$\text{CH}_3-\text{CH}_2-\text{COH}-\text{CH}_2\text{OC}_6\text{H}_5$	131	1.0199	1.5098	52.80	52.65	73.32	73.39	$\text{C}_{11}\text{H}_{16}\text{O}_2$	73.30	8.95
Hydrogenation products of phenol and isoprene oxide addition product (principal fraction: 97.2% H <sub>2</sub> absorbed)	131	1.0210	1.5101	52.74	52.65	73.58	73.60	$\text{C}_{11}\text{H}_{16}\text{O}_2$	73.30	8.95

at 150-160°C for four hours. The yield of the acetal of  $\alpha$ -phenoxybutyric aldehyde was 50 g; b.p. 141-143°C (10 mm). The  $\alpha$ -phenoxybutyric aldehyde prepared from it by hydrolysis in the presence of dilute sulfuric acid had the following constants:

B. p. 118-119° (10 mm),  $d_4^{20}$  1.0431,  $n_D^{20}$  1.5130, MR 46.80; calc. 46.43.

Found %: C 73.30, 73.54; H 7.45, 7.41.  $C_{10}H_{12}O_2$ . Calculated %: C 73.14; H 7.37.

A solution of 4 g of  $\alpha$ -phenoxybutyric aldehyde in 15 ml of ether was added drop by drop to an ether solution of lithium aluminum hydride (calculated quantity) at such a rate that the ether boiled gently. Within 15 minutes after completion of the reaction, 5 ml of water and 30 ml of 10% sulfuric acid were added to the reaction flask. The ether extract was dried over sodium sulfate. The constants of the product obtained are shown in Table 2.

1-Phenoxy-2-methylbutanol-2. Phenoxyacetone, 18 g, prepared from bromacetone [15] and dissolved in 25 ml of absolute ether was added drop by drop, with stirring and cooling, to an ether solution of ethyl magnesium bromide (from 8 g of magnesium). The reaction mixture was allowed to stand overnight and then was heated until the ether boiled gently for three hours, after which the mixture was decomposed with 10% hydrochloric acid. The constants and analytical data on the substance obtained are shown in Table 2.

#### SUMMARY

1. The addition of phenols (phenol, o- and p-chlorophenol) to divinyl, chloroprene and isoprene oxides was studied.
2. It was found that the principal products of the reaction in all cases are primary phenyl ethers of the corresponding glycols. The largest quantity of the second possible isomer (secondary ether) is obtained in the case of chloroprene oxide.
3. It was shown that substituted phenols combine with chloroprene oxide with the formation of isomeric ethers in a somewhat different ratio than unsubstituted phenol does.
4. Isomeric phenyl ethers of butanediol-1, 2 and 2-methylpropanediol-1, 2 (primary ether) were prepared in a pure state for purposes of identification.

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## STUDIES OF THE STRUCTURE OF UNSATURATED NITRO COMPOUNDS BY THE METHOD OF DIPOLE MOMENTS\*

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A study of the dipole moments of unsaturated nitro compounds gave valuable information about their structure (configuration and disposition of electron densities) and aided in evaluating their ability to react with nucleophilic and electrophilic reagents. The dipole moments of unsaturated nitro compounds had not been systematically studied [1, 2].

The nitroalkenes and aryl nitroalkenes which were studied by us for the first time (Table 1) might be assigned either a plane (cis, trans) or a noncoplanar configuration.

The cis-structure is excluded because of considerable steric hindrance which occurs as a result of the superimposing of a hydrogen atom of the benzene ring and an oxygen of the nitro group in  $\beta$ -nitrostyrenes.

Thus, in cis- $\beta$ -nitrostyrene and its derivatives, using the generally accepted values for the angles and bond lengths as shown in Fig. 1, the distance between the centers of an atom of hydrogen of the phenyl group and an atom of oxygen of the nitro group amounts to only  $\sim 0.3$  Å and the cis-form can occur only under the condition where the nitro group is drawn out of the surface of the phenyl ring.

An analogous situation occurs in the geometry of  $\alpha$ -furyl- $\beta$ -nitroethylene and its derivatives. According to Fig. 2, the distance between the centers of unlinked valence atoms of hydrogen and oxygen is only about 0.5 Å for the cis-form; the atoms are practically superimposed on one another.

The dislocation of coplanarity as a result of drawing a nitro group out of the plane of the benzene ring must hinder the energetically favorable  $\pi$ -linking in  $\beta$ -nitrostyrenes and furylnitroethylene and cause their moments to approach the moments of aliphatic nitro compounds, which does not occur. Consequently the hypothesis in regard to the noncoplanarity of the substances under investigation must also be abandoned.

The closeness of the measured moments and vector sums of the moments of individual bonds and the absence of steric hindrances permits us to assign a trans-structure to the  $\beta$ -nitrostyrenes.

Thus, the calculated vector sum of the moments of p-dimethylamino- $\beta$ -nitrostyrene (VI)  $\mu_E$  for the trans-form is 6.12 D ( $m_1 = 1.61$  D,  $m_2 = 4.51$  D,  $\theta = 0^\circ$ ); for the cis-form it is  $-3.84$  D ( $\theta = 120^\circ$ ); the experimental value  $\mu = 7.61$  D corresponds better with the trans-form.

For p-nitro- $\beta$ -nitrostyrene (VII)  $\mu_E$  for the cis-form is 7.38 D ( $m_1 = 4.01$  D,  $m_2 = 4.51$  D,  $\theta = 60^\circ$ ); for the trans-form it is 0.50 D ( $\theta = 180^\circ$ ); the experimental value of  $\mu = 1.00$  D.

There are two possibilities for the spatial disposition of nitrovinyl groups relative to the benzene ring in 1,4-bis-( $\beta$ -nitrovinyl)-benzene (X): the trans or cis-configuration.\*\* For the trans-form the dipole moment of the molecule must be equal to zero because of the complete compensation of the moments of the individual bonds.

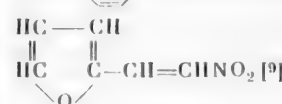
In the case of the cis-position of the nitrovinyl groups, however, there should be a small dipole moment of the molecule as a consequence of two possible reasons: partial compensation of the moments of the nitrovinyl groups, i.e., their addition at an obtuse angle less than  $180^\circ$ , and the greater polarity of the C-H bond at an  $\alpha$ -carbon atom

\* For the previous report see ZhOKh 31, 1528 (1961).

\*\* In a permanent trans-position of the nitro group and the benzene ring relative to the C = C bond, since the cis-position of these groups is excluded for the reasons mentioned above.

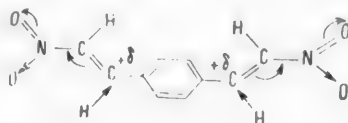
of the nitrovinyl group which is caused by the greater electron gap (+  $\delta$ ) than the polarity of the corresponding bond at the  $\beta$ -carbon.

TABLE 1. Experimental Values for Polarization and Dipole Moments

No.	Compound	M. p.	$P_{\infty}$	$P_E$	$P_A$	$\mu$ (D)
I	$\text{CH}_2=\text{CHNO}_2$ [3]	B. p. 36° (100 mm)	261.9	17.5	3.9	3.41
II	$\text{C}_6\text{H}_5-\text{CH}=\text{CH}_2$	B. p. 146°	—	—	—	0.12[4]
III	$\text{C}_6\text{H}_5-\text{CH}=\text{CHNO}_2$ [5]	58–59°	472.1	42.9	7.9	4.51
IV	$\text{CH}_3-\text{C}_6\text{H}_4-\text{CH}=\text{CHNO}_2$ [6]	101	574.1	47.5	8.8	5.00
V	$\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{CH}=\text{CHNO}_2$ [7]	87	665.9	49.1	7.4	5.43
VI	$(\text{CH}_3)_2\text{N}-\text{C}_6\text{H}_4-\text{CH}=\text{CHNO}_2$ [8]	184	1260.7	56.0	8.4	7.61
VII	$\text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{CH}=\text{CHNO}_2$ [8]	206–207	81.8	49.4	11.8	1.00
VIII	 $\text{C}-\text{CH}=\text{CHNO}_2$ [9]	75	568.1	34.5	7.9	5.00
IX	$\text{O}_2\text{NCH}=\text{CH}-\text{CH}=\text{CHNO}_2$ [10]	147–148	59.0	32.9	15.8	0.71
X	$\text{O}_2\text{NCH}=\text{CH}-\text{C}_6\text{H}_4-\text{CH}=\text{CHNO}_2$ [11]	231–232	96.6	58.2	15.8	1.05
XI	$\text{O}_2\text{NHC}=\text{CH}-\text{C}_6\text{H}_4-\text{CH}=\text{CHNO}_2$ [12]	201–203	349.4	58.2	15.8	3.65

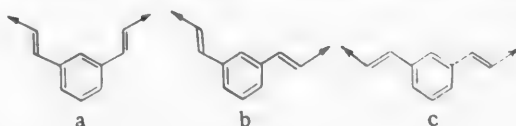
Note:  $P_{\infty}$  is the molar polarization of the compound at infinite dilution;  $P_E$  is the electron polarization;  $P_A$  is the atomic polarization.

Consequently, the fact that this compound has a small moment (1.05 D) is in favor of the cis-position of the nitrovinyl groups relative to the benzene ring, and also indicated that the nitrovinyl group, unlike the nitro group, is not regular, i.e., the vector of its moment deviates from the direction of the  $\text{C}_{\text{ar}}-\text{C}_{\alpha}$  bond.



In accordance with the same considerations, the fact that 1,4-dinitrobutadiene-1,3 has a moment of  $\mu = 0.71$  D indicates the probability of its having a cis-structure.

There are three possible positions of the nitrovinyl group in 1,3-bis( $\beta$ -nitrovinyl)-benzene (XI):



The direction of the moments of the nitro groups themselves in all three cases amounts to  $120^\circ$ , so that, if the nitrovinyl group were regular, the moment in all three cases would be equal to 4.3 D, i.e., to the moment of nitrostyrene (4.51 D) decreased by approximately 0.2 D, as in the case of *m*-dinitrobenzene and nitrobenzene (3.8 as compared with 4.01 D). However, insofar as the nitrovinyl group is actually irregular, it is possible to differentiate case a from b and c. In case a the angle between the corresponding moments must be less than, in case b equal to, and in case c greater than  $120^\circ$  and the total moment correspondingly greater, equal or less than the value 4.3 D estimated above. The experimental value  $\mu$ , 3.65 D points in favor of structure c.

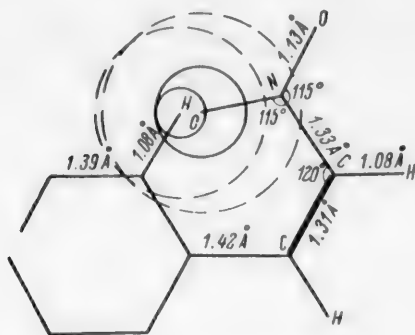


Figure 1. Cis- $\beta$ -nitrostyrene.

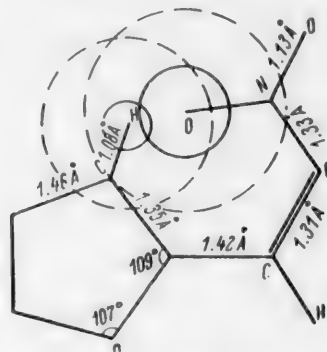
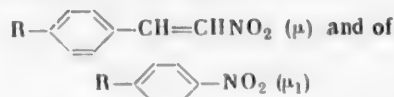


Figure 2. Cis- $\alpha$ -furyl- $\beta$ -nitroethylene.

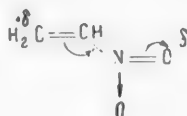
The linking of the nitro group with a double bond and an aromatic residue results in the appearance of a supplementary moment of the molecule—the linking moment  $\mu_c$ —which by vector addition with the sum of the moments of the individual bonds ( $\mu_E$ ), must give the observed dipole moment ( $\mu$ ).

TABLE 2. Magnitude of the Dipole Moment of



R	$\mu$	$\mu$	$\Delta\mu$
H	4.51	4.01 [1]	0.50
CH <sub>3</sub>	5.00	4.44	0.56
CH <sub>3</sub> O	5.43	4.75 [14]	0.68
(CH <sub>3</sub> ) <sub>2</sub> N	7.61	7.07 [14]	0.54

The moment of nitroethylene (3.41 D), which is larger by 0.21 D than that of nitromethane (3.20 D), results from the  $\pi, \pi$ -linking.



As might be expected, the dipole moments increase in the series: ethylene (3.41 D) < nitrobenzene (4.01 D) < nitrostyrene (4.51 D) in consequence of the lengthening of the linking branch and an increase in the number of  $\pi$ -electrons in the conjugated system.

For the same reasons the dipole moments of  $\beta$ -nitrostyrenes with nucleophilic substituents in the para position are larger than the moments of the corresponding benzene derivatives (Table 2).

## EXPERIMENTAL

The dipole moments were measured in benzene at 25° by the pulsation method. The results of the measurements are shown in Tables 1 and 2. The electron polarization ( $P_E$ ) was taken as equal to the molar refraction  $MR_D$  and was calculated additively as the sum of the refraction of the atoms and of the bonds for the D-line of sodium; the atomic polarization ( $P_A$ ) was calculated by the additive rule introduced by one of us [15] in which the group increments are taken as follows:  $NO_2-3.9 \text{ cm}^3$ ,  $-CH=CHNO_2-7.9 \text{ cm}^3$ ,  $CH_3-0.9 \text{ cm}^3$ . In certain cases (compounds V and VI), when it was not possible to calculate the value of  $P_A$  by this means,  $P_A$  was assumed to be approximately equal to  $0.15 MR_D$ ; this is completely justified for large dipole moments.

The dipole moment (in Debyes) may be calculated in accordance with the formula:

$$\mu = 0.0127 \sqrt{(P_\infty - P_E - P_A) T}$$

or, for 25°:

$$\mu = 0.220 \sqrt{P_\infty - P_E - P_A}$$

The compounds studied were synthesized by established procedures [3,5-12] and carefully purified.

## SUMMARY

1. The trans configuration of  $\beta$ -nitrostyrene and some of its substituents in the ring was determined by the method of dipole moments.
2. It was shown that in 1, 4-bis ( $\beta$ -nitrovinyl)-benzene, and by analogy in 1, 4-dinitrobutadiene-1, 3 nitrovinyl residues are located in a cis-position relative to the benzene ring and a single bond.
3. Increase of the dipole moments in the series nitroethylene-nitrobenzene- $\beta$ -nitrostyrene is explained by an increase in the effect of conjugation.

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A STUDY OF THE INFLUENCE OF STERIC FACTORS  
ON CONJUGATION IN MOLECULES OF UNSATURATED  
NITRO COMPOUNDS BY THE METHOD OF DIPOLE MOMENTS

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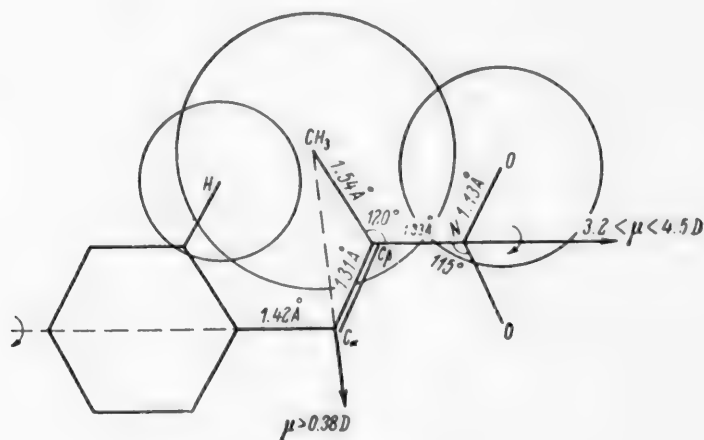
In a study of the dipole moments of some methyl homologs of  $\beta$ -nitrostyrenes and bis( $\beta$ -nitrovinyl)-benzenes, we found that substitution of an atom of hydrogen at the  $\beta$ -carbon of  $\beta$ -nitrostyrenes by a methyl group led to a decrease in the dipole moments by  $\sim 0.4D$  (Table 1).

In  $\beta$ -methyl- $\beta$ -nitrostyrenes in consequence of the superposition of a methyl group (van der Waals radius  $\sim 2 \text{ \AA}$ ) and a hydrogen atom in the orthoposition in the benzene ring, and also a nitro group, the coplanarity of the molecule is disrupted—the benzene ring, the methylvinyl group and the nitro group get out of one plane (turning on the axes  $C_{Ar}-C_{\alpha}$  and  $C_{\beta}-N$ ) (see figure).

As a result of the disruption of coplanarity there is a weakening of the  $\pi$ -linking in  $\beta$ -methyl- $\beta$ -nitrostyrenes with the benzene ring and the vinyl and nitro groups; however, the less effective  $\pi, \sigma$ -linking of the C-H bonds of the methyl group and of the double bonds of the vinyl residue is preserved.

As is well known, the magnitude of the dipole moment is the result of the vector addition of the moments of individual polar bonds and groups, and of the dipole moment resulting from conjugation. Therefore a weakening of conjugation naturally leads to a decrease in the observed dipole moments. This decrease results from the following reductions: 1) of the transverse moment to a magnitude lying between 4.5 and 3.2 D (a weakening of the linking of the nitro group to the remaining part of the molecule); 2) of the longitudinal moment (disruption of the linking of the vinyl group with the benzene ring causing a decrease in the polarity of the styrene residue; its  $\mu \approx 0.12D$ ).

At the same time the component of the moment resulting from the linking of the C-H bonds of the methyl group and of the double bonds of the vinyl group is preserved. It must be not less than the moment of propylene



$\beta$ -Methyl- $\beta$ -nitrostyrene

# Dipole Moments of $\beta$ -Nitrostyrenes and $\beta$ -Methyl- $\beta$ -nitrostyrenes

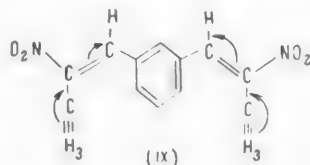
Formula	R = CH <sub>3</sub>						R = H		$\mu - \mu_1$
	No.	m. p.	$P_\infty$	$P_E$	$P_A$	$\mu$	No.	$\mu_1$	
<chem>Cc1ccc(cc1)C=C(R)[N+](=O)[O-]</chem> [I]	I	65–66°	411.3	47.5	8.8	4.14	Ia	4.51	–0.37
<chem>Cc1ccc(cc1)C=C(R)[N+](=O)[O-]</chem> [II]	II	52–53	490.7	52.1	9.7	4.55	IIa	5.00	–0.45
<chem>COc1ccc(cc1)C=C(R)[N+](=O)[O-]</chem> [III]	III	43–44	596.3	53.1	8.1	5.09	IIIa	5.43	–0.34
<chem>CN(C)c1ccc(cc1)C=C(R)[N+](=O)[O-]</chem> [IV]	IV	123.5–124	1135.5	60.7	9.1	7.18	IVa	7.61	–0.43
<chem>[O-][N+](=O)c1ccc(cc1)C=C(R)[N+](=O)[O-]</chem> [V]	V	114–115	70.3	54.0	12.7	0.41	Va	1.00	–0.59
<chem>Cc1ccc(cc1)C=C(R)[N+](=O)[O-]</chem> [VI]	VI	67–68	398.8	50.6	9.5	4.05	—	—	—
<chem>Cc1ccc(cc1)C=C(R)[N+](=O)[O-]</chem> [VII]	VII	74–75	512.6	38.5	8.8	4.59	VIIa	5.00	–0.41
<chem>[O-][N+](=O)C=C(R)c1ccc(cc1)C=C(R)[N+](=O)[O-]</chem> [VIII]	VIII	122–123	141.3	67.4	17.6	1.65	VIIIa	1.05	+0.60
<chem>[O-][N+](=O)C=C(R)c1ccc(cc1)C=C(R)[N+](=O)[O-]</chem> [IX]	IX	108–109	448.1	66.1	17.6	4.20	IXa	3.65	+0.55

Note:  $P_\infty$  is the molar polarization of the compound at infinite dilution;  $P_E$  is the electron polarization;  $P_A$  is the atomic polarization.

J.38 D) and directed along the line of the  $C_\beta$ –CH<sub>3</sub> bond with the positive end at the methyl group.

In  $\beta$ -bromo- $\beta$ -nitrostyrene (VI), despite considerable steric hindrance caused by the bromine atom, the observed moment (4.05 D) was practically identical with that calculated by the vector sum (4.0 D). A decrease in the moment is apparently compensated for at the expense of the  $\pi$ ,  $\sigma$ -linking of the styrene residue with a bromine atom.

In 1,4- and 1,3-bis( $\beta$ -nitro- $\beta$ -methylvinyl)-benzenes (VIII, IX), the role of the  $\pi$ ,  $\sigma$ -linking of the methyl groups with the ethylene residue becomes decisive; the geometry of compounds (VIII) and (IX) is similar to the geometry of 1,4- and 1,3-bis( $\beta$ -nitrovinyl)-benzenes (VIIIa, IXa) which have a cis-configuration [1] relative to the benzene ring. Therefore the addition of the transverse moments of the nitrovinyl groups gives the observed dipole moment which is naturally larger than that of compounds (VIIIa) and (IXa).



These data are in accordance with the results of a study of the combination dispersion spectra of the aryl nitroalkenes [2].

In  $\beta$ -methyl homologs of  $\beta$ -nitrostyrenes and bis( $\beta$ -nitrovinyl)-benzenes, because of the disruption of coplanarity and linking, a decrease in the bands of the nitro group, the double bond and the benzene ring is observed.

The apparent discrepancy between the decrease in the intensity of the bands and the increase in the dipole moments as a result of the introduction of the methyl group into the  $\beta$ -carbon atom of 1,4- and 1,3-bis( $\beta$ -nitrovinyl)-benzenes (VIII, IX) is easily explained by the fact that the  $\pi$ ,  $\sigma$ -linking of the methyl group and a double bond, which affects the magnitude of the dipole moments, does not affect the intensities of the bands of the combination dispersion spectra, which are dependent primarily on the  $\pi$ -linking.

#### EXPERIMENTAL

The method of measurement is described in a previous communication [1]; the results are shown in the table.

#### SUMMARY

1. The dipole moments of  $\beta$ -methyl homologs of  $\beta$ -nitrostyrenes are lower than those of the  $\beta$ -nitrostyrenes because of the disruption of coplanarity and weakening of the  $\pi$ -linking.

2. The increase of the dipole moments as a result of the introduction of methyl groups on the  $\beta$ -carbons of 1,4- and 1,3-bis( $\beta$ -nitrovinyl)-benzenes is determined by the  $\pi$ ,  $\sigma$ -linking of the bonds of the methyl groups and the double bonds of the vinyl residue.

3. The absence of synchronism in the changes of the dipole moments and the intensities of the bands of the combination dispersion spectra of the aryl nitroalkenes was demonstrated.

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# STUDIES OF THE LIPIDS

## VII. THE SYNTHESIS OF SOME TRIGLYCERIDES OF LINSEED AND SOY OILS

T. K. Mitrofanova, E. N. Zvonkova, I. K. Sarycheva,

S. P. Ivashchenko, and N. A. Preobrazhenskii

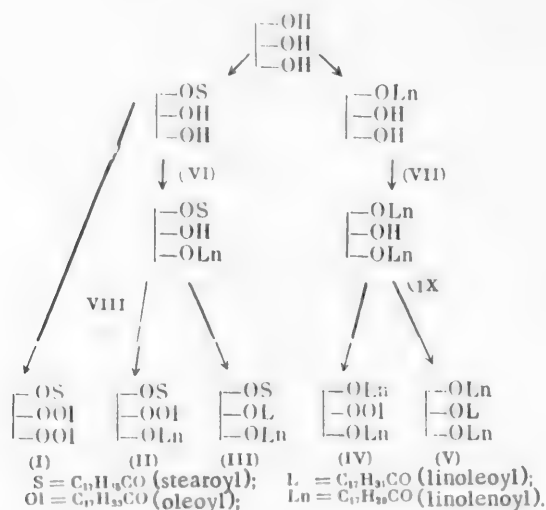
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pp. 2178-2180, July, 1961

Original paper submitted June 25, 1960

The present paper describes the synthesis and fundamental physico-chemical properties of  $\alpha$ -stearoyl- $\beta$ , $\alpha'$ -diolein (I),  $\alpha$ -stearoyl- $\beta$ -oleoyl- $\alpha'$ -linolenoin (II),  $\alpha$ -stearoyl- $\beta$ -linoleoyl- $\alpha'$ -linolenoin (III),  $\alpha$ , $\alpha'$ -dilinolenoyl- $\beta$ -oleoin (IV),  $\alpha$ , $\alpha'$ -dilinolenoyl- $\beta$ -linoleoin (V), which, together with the compounds previously described by us, are components of vegetable oils, especially flaxseed and soy oils [1-5].



The synthesis of these compounds is based on the reaction of the chlorides of stearic and linolenic acids with glycerine, two ( $\alpha'$  and  $\beta$ ) hydroxyl groups of which are given preliminary protection by means of acetone, which is carried through the stage of preparation of the monoglycerides:  $\alpha$ -stearin (VI) and  $\alpha$ -linolenoin (VII). Conversion of the monoglycerides into the triglycerides may be accomplished either in one step—for the synthesis of compound (I), or in two steps—for compounds (II), (III), (IV) and (V), through  $\alpha$ -stearoyl- $\alpha'$ -linolenoin (VIII) and  $\alpha$ , $\alpha'$ -dilinolenoin (IX).

### EXPERIMENTAL

$\alpha$ -Stearoyl- $\beta$ ,  $\alpha'$ -diolein (I). 31.8 g of the chloride of oleic acid (b. p. 140-142° at 0.5 mm) were added during the course of 30 minutes at 0° to a mixture of 19.0 g of  $\alpha$ -monostearoin (VI) and 41.0 g of quinoline. The reaction mixture was heated at the boiling point in a current of nitrogen for five hours, then cooled to 5-6°; 200 ml

of ether were added and the solution made acid by the addition of 100 ml of 10% sulfuric acid. The upper layer was separated, washed with a saturated solution of sodium bicarbonate and dried over sodium sulfate. The solvent was removed in vacuo (20 mm). The remaining material was washed with 90 ml of methyl alcohol at 40°. 24.45 g of crude triglyceride was obtained, which was dissolved in 120 ml of anhydrous acetone and passed through a layer of activated carbon (15 × 10 mm) and aluminum oxide (15 × 15 mm) and twice recrystallized at 55-60°. The yield was 17.2 g (27.5%). M. p. 21-21.5°.

Found %: C 77.08; H 11.63. Iodine number 58.10.  $C_{57}H_{106}O_6$ . Calculated %: C 76.92; H 12.04. Iodine number 57.22.

$\alpha$ -Stearoyl- $\beta$ -oleoyl- $\alpha'$ -linolenoin (II). 3.0 g of the chloride of oleic acid were added to a mixture of 4.5 g of  $\alpha$ -stearoyl- $\alpha'$ -linolenoin (VIII) and 1.63 g of quinoline in 30 ml of chloroform. The reaction mixture was heated to boiling in a current of nitrogen for four hours, after which it was cooled to 5-10°. Then 200 ml of ether were added and it was acidified with 25 ml of 10% sulfuric acid. The upper layer was separated, washed with 20 ml of a 10% aqueous solution of potassium carbonate and dried over sodium sulfate. The solvent was removed in vacuo (12 mm) in a current of nitrogen. The remaining material was washed with 70 ml of alcohol at 18° and 50 ml at 60°, after which it was dissolved in 50 ml of anhydrous acetone and passed through a layer of activated carbon (20 × 50 mm), cooled to -65° and allowed to stand under these conditions for 30-35 minutes. The precipitate was filtered off from the mother liquor and recrystallized from 25 ml of acetone. The substance that crystallized at -12- -10° was filtered from the liquid phase. The mother liquor was cooled to -20° and stirred for two hours at this temperature. To the precipitate thus obtained, after removal of the acetone, were added 30 ml of anhydrous ether and the solution passed through a chromatographic column containing aluminum oxide (20 × 100 mm); it was elutriated with 200 ml of ether and then the solvent was removed. The yield was 3.1 g (47.4%).

M. p. -3- -2°,  $d_4^{20}$  0.9211,  $n_D^{20}$  1.4707,  $MR_D$  268.12.  $C_{57}H_{102}O_6 F_4$ . Calculated 268.52.

Found %: C 77.58; H 11.36. Iodine number 112.5.  $C_{57}H_{102}O_6$ . Calculated %: C 77.55; H 11.56. Iodine number 114.9.

$\alpha$ -Stearoyl- $\beta$ -linoleoyl- $\alpha'$ -linolenoin (III). The synthesis was conducted under the conditions of the preceding experiment, using 13.0 g of  $\alpha$ -stearoyl- $\alpha'$ -linolenoin (VIII) in 60 ml of chloroform and 7.7 g of the chloride of linoleic acid (b. p. 157-158° at 0.6 mm) in the presence of 3.5 g of quinoline. After removal of impurities by means of methyl alcohol (three times, 50 ml each) the product was recrystallized from a fivefold quantity of acetone at -35-30°. The yield was 6.45 g (34.6%).

M. p. -10.2-9.5°,  $d_4^{20}$  0.9199,  $n_D^{20}$  1.4763,  $MR_D$  270.3  $C_{57}H_{100}O_6 F_5$ . Calculated 268.05.

Found %: C 77.38; H 11.33. Iodine number 148.1.  $C_{57}H_{100}O_6$ . Calculated %: C 77.67; H 11.43. Iodine number 144.0.

$\alpha$ - $\alpha'$ -Dilinenoyl- $\beta$ -oleoin (IV). 16.9 g of crude product were obtained by the method used for the synthesis of  $\alpha$ -stearoyl- $\beta$ -oleoyl- $\alpha'$ -linolenoin (II) from 11 g of  $\alpha$ - $\alpha'$ -dilinenonoin (IX), 7.4 g of the chloride of oleic acid and 10.3 g of quinoline in 50 ml of chloroform. This was washed with anhydrous methyl alcohol which was heated to 40-50° (three times, 25 ml each) and recrystallized from 60 ml of acetone at -45- -40°. The yield was 4.0 g (25.6%).

M. p. -22- -21°, -13- -12°,  $d_4^{20}$  0.9248,  $n_D^{20}$  1.4767,  $MR_D$  267.6.  $C_{57}H_{96}O_6 F_7$ , calculated 267.12.

Found %: C 78.37; H 10.62. Iodine number 201.9.  $C_{57}H_{96}O_6$ . Calculated %: C 78.03; H 11.03. Iodine number 202.5.

$\alpha$ , $\alpha'$ -Dilinenoyl- $\beta$ -linoleoin (V). 3.0 g of crude product were obtained from 2.03 g of  $\alpha$ , $\alpha'$ -dilinenonoin (IX) and 2.15 g of the chloride of linoleic acid in 10 ml of chloroform in the presence of 0.9 g of quinoline. This was chromatographed twice [6] in a column containing silicic acid (30 g of silicic acid per gram of product). The yield was 1.42 g (49.5%).

M. p. -16- -15°,  $d_4^{20}$  0.9319,  $n_D^{20}$  1.4775,  $MR_D$  265.7.  $C_{57}H_{94}O_6 F_8$ . Calculated: 266.65.

Found %: C 78.31; H 10.81. Iodine number 234.1.  $C_{57}H_{94}O_6$ . Calculated %: C 78.21; H 10.82. Iodine number 232.1.

#### SUMMARY

The synthesis of the following products was achieved:  $\alpha$ -stearoyl- $\beta$ , $\alpha'$ -diolein,  $\alpha$ -stearoyl- $\beta$ -oleoyl- $\alpha'$ -linolenin,  $\alpha$ -stearoyl- $\beta$ -linoleoyl- $\alpha'$ -linolenin,  $\alpha$ , $\alpha'$ -dilinoloyl- $\beta$ -olein,  $\alpha$ , $\alpha'$ -dilinolenoyl- $\beta$ -linolein.

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# STUDIES OF THE LIPIDS

## VIII. THE SYNTHESIS OF $\alpha, \beta$ -DILINOLEOIN

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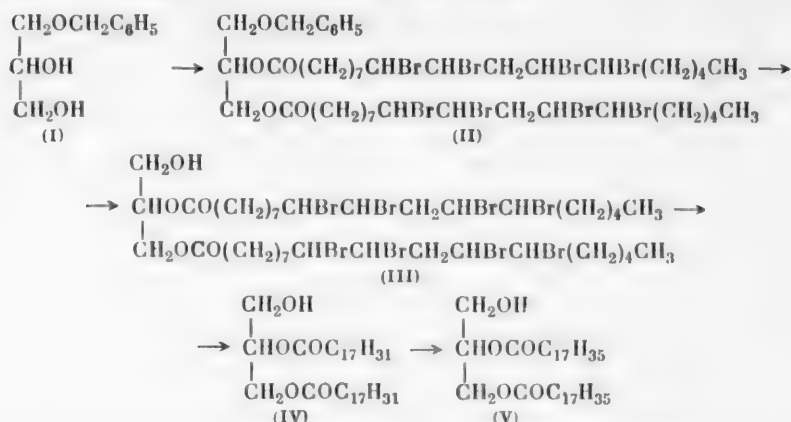
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$\alpha, \beta$ -Diglycerides [1] are of interest as fundamental intermediates in the synthesis of complex lipids and triglycerides which enter into the composition of animal and plant cells.

The present paper describes the preparation of  $\alpha, \beta$ -dilinolein [2]. The method by which the synthesis is carried out [3] differs from those previously described [4] in that it offers the possibility of preparing completely unsaturated  $\alpha, \beta$ -diglycerides containing the same or different acid residues.



$\alpha$ -Benzylglycerin (I) was acylated by the chloride of 9, 10, 12, 13-tetrabromostearic acid and the benzyl group removed in the presence of palladium black. The bromine was removed by activated zinc. Debromination occurs without isomerization [3,5]. Purification of the product (IV) was accomplished over silicic acid. In order to confirm the structure of  $\alpha, \beta$ -dilinolein (IV), it was converted into distearoin [6] (V).

The infrared spectra [7] of diglycerides (IV) and (V) are practically identical, with the exception of a supplementary absorption band at  $3020\text{ cm}^{-1}$  in the spectrum of compound (IV) which is caused by the presence of double bonds in its molecule.

A band for the OH group was found at  $3160\text{ cm}^{-1}$  and for the  $>\text{C}=\text{O}$  group at  $1735\text{ cm}^{-1}$ . No band at  $970\text{--}990\text{ cm}^{-1}$  for the trans double bonds was found. This indicates that bromination and debromination proceed without isomerization and that the acyl residues in the molecule of compound (IV) have the structure that is characteristic of natural compounds.

### EXPERIMENTAL

**9,10,12,13-Tetrabromostearic acid.** 36.1 ml of bromine was added, during the course of 30 minutes, with stirring, to a solution of 100 g of linoleic acid in 200 ml of chloroform at  $10\text{--}15^\circ\text{C}$ . The chloroform was distilled off. The remaining material (169 g) was recrystallized twice from dichloroethane (80 and 75 ml). The yield was 58 g (27.2%). M. p.  $115\text{--}116^\circ\text{C}$ . [8].

**The chloride of 9,10,12,13-tetrabromostearic acid.** During the course of 15 minutes, 17 ml of thionyl chloride was added to a solution of 60.0 g of 9,10,12, 13-tetrabromostearic acid in 200 ml of toluene at  $0^\circ\text{C}$ . The reaction mixture was heated for three hours at  $70^\circ\text{C}$  with energetic stirring. The remainder of the thionyl chloride and the solvent were distilled off. The yield was 61.8 g (99.8%). M. p.  $56\text{--}57^\circ\text{C}$ .

Five g of the product was recrystallized from 30 ml of methyl alcohol. The colorless crystalline substance was easily soluble in chloroform, acetone, toluene, and moderately soluble in ethyl and methyl alcohols. The yield was 4.1 g. M. p. 58-59° [9].

Found %: C 35.35; H 5.03.  $C_{18}H_{31}OClBr_4$ . Calculated %: C 34.96; H 5.02.

$\alpha, \beta$ -Di-9, 10, 12, 13-tetrabromostearoyl- $\alpha'$ -benzylglycerine (II). During the course of 30 minutes a solution of 61.85 g of the chloride of tetrabromostearic acid in 70 ml of chloroform was added to a mixture of 8.15 g of  $\alpha$ -benzylglycerine [10] and 13.1 ml of quinoline at 0°, with stirring. Stirring was continued for 48 hours at 40°. The mixture was diluted with 800 ml of ether and washed with 150 ml of 0.5 N sulfuric acid and a saturated aqueous solution of sodium bicarbonate. The ether solution was cooled to -5° and within 24 hours the precipitate formed was filtered off. The yield was 44.3 g (72.5%), M. p. 60-62°.

Five g of this product was recrystallized twice from ether (15 ml, 11 ml). It was a colorless crystalline substance, easily soluble in chloroform, acetone and cyclohexane, moderately soluble in ether, methyl and ethyl alcohol and acetic acid, and insoluble in water. The yield was 3.63 g. M. p. 67.5-68°C.

Found %: C 41.19; H 5.60; Br 47.52.  $C_{46}H_{74}O_5Br_8$ . Calculated %: C 41.08; H 5.54; Br 47.68.

$\alpha, \beta$ -Di-9, 10, 12, 13-tetrabromostearoin (III). A solution of 20.5 g of product (II) in 250 ml of a mixture of glacial acetic acid and cyclohexane (4:1) was agitated with 3.8 g of palladium black [11] in an atmosphere of hydrogen at 20° under a 40-70 cm water column until absorption of hydrogen ceased. The hydrogenation required one hour and 45 minutes; 370 ml of hydrogen were absorbed (theoretical: 335 ml). The catalyst was filtered off, washed with 40 ml of a mixture of glacial acetic acid and cyclohexane (4:1) and the liquid evaporated in vacuo. The material remaining was dissolved in 300 ml of chloroform and washed with a saturated aqueous solution of sodium bicarbonate. The chloroform was driven off, and the residue dried for two hours at 0.1 mm. The yield was 18.95 g (97.8%). M. p. 70-72°.

3.7 g of compound (III) were recrystallized twice from methyl alcohol (22 ml, 19 ml). It was a colorless, crystalline material, easily soluble in chloroform, acetone and acetic acid, and moderately soluble in ethyl and methyl alcohol. The yield was 2.5 g. M. p. 71-72°.

Found %: Br 50.52.  $C_{39}H_{68}O_5Br_8$ . Calculated %: Br. 50.90.

$\alpha, \beta$ -Dilinolein (IV). During the course of 30 minutes, 75 g of activated zinc dust [3] were added, with stirring, to a solution of 15.2 g of compound (III) in 200 ml of acetone. The reaction mixture was heated for 30 minutes at 40° and at the boiling point for one hour. The acetone was driven off. The remaining material was dissolved in 350 ml of peroxide-free ether, washed with water until the reaction for Br<sup>-</sup> was negative, and dried over sodium sulfate. The ether was removed and the residue (6.2 g) was dissolved in 60 ml of petroleum ether (b. p. 40-60°) and passed through a column (2 x 50 cm) containing silicic acid. The column was washed with 350 ml of petroleum ether. The  $\alpha, \beta$ -dilinolein was washed with 350 ml of a mixture of petroleum ether and ether (1:1) and evaporated in vacuo. The residue was dissolved in 110 ml of acetone, allowed to stand for twelve hours at -7° and a small quantity of impurity removed. The solution was then cooled to -75° and allowed to stand for one hour at this temperature. A precipitate was separated and was freed from traces of solvent at 0.1 mm. The product was a mobile yellow oil which was soluble in chloroform, ether, petroleum ether and acetone, and insoluble in water. The yield was 4.4 g (59.2%).

$d_4^{20}$  0.9421,  $n_D^{20}$  1.4832,  $M_R$  182.9.  $C_{39}H_{68}O_5F_4$ . Calculated: 182.74.

Found %: C 76.39; H 10.80. Iodine number 162.2, 162.6.  $C_{39}H_{68}O_5$ . Calculated %: C 76.12; H 11.00. Iodine number 164.0.

$\alpha, \beta$ -Distearoin (V). A solution of 1 g of compound (IV) in 25 ml of glacial acetic acid was stirred with 0.2 g of platinum oxide in an atmosphere of hydrogen at 20° under a 40-60 cm water column until absorption of hydrogen ceased. Hydrogenation continued for 50 minutes and 140 ml of hydrogen were absorbed (theoretical: 145 ml). The catalyst was filtered off, and washed with 5 ml of glacial acetic acid. It was evaporated in vacuo and the residue dissolved in 70 ml of chloroform, washed with a saturated aqueous solution of sodium bicarbonate and dried over sodium sulfate. The chloroform was removed. The yield was 0.93 g (98.9%). M. p. 71-72°. The product was recrystallized from 17 ml of a mixture of chloroform and petroleum ether (b. p. 40-60°) (2:3). The yield was 0.71 g (69.3%). M. p. 71.5-72° [6].

# SUMMARY

1. The synthesis of  $\alpha$ ,  $\beta$ -dilinolein was accomplished.
2. During the course of the synthesis,  $\alpha$ ,  $\beta$ -di-9, 10, 12, 13-tetrabromostearoyl- $\alpha'$ -benzylglycerin and  $\alpha$ ,  $\beta$ -di-9, 10, 12, 13-tetrabromostearoin were separated and characterized.
3. The structure of  $\alpha$ ,  $\beta$ -dilinolein was confirmed by reducing it catalytically to  $\alpha$ ,  $\beta$ -distearoin.

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# STUDIES OF COMPLEX LIPIDS

## II. THE SYNTHESIS OF UNSATURATED AND SATURATED $\alpha$ -KEPHALINS

V. I. Shvets, L. V. Volkova, and N. A. Preobrazhenskii

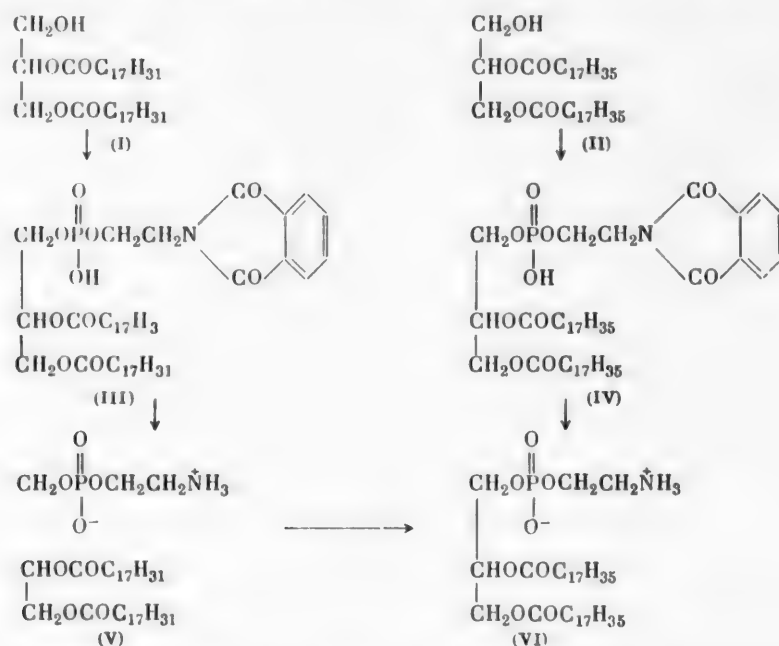
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The present paper describes the preparation of an unsaturated natural glycerine phosphatide [1]—dilinoleoyl- $\alpha$ -kephalin—starting from  $\alpha, \beta$ -dilinoleoin, which was previously synthesized by us [2]. The method proposed by Rose for saturated  $\beta$ -kephalins [3] and used by a number of authors [4-6] was utilized for this synthesis.



$\alpha, \beta$ -Dilinoleoin (I) and  $\alpha, \beta$ -distearoin (II) condense with the dichloride of  $\beta$ -phthalimidoethylphosphoric acid in the presence of triethylamine. The chloro derivative is saponified by water. Dilinoleoyl-N-phthalimido- $\alpha$ -kephalin (III) is obtained in pure form by chromatography over silicic acid, and distearoyl-N-phthalimido- $\alpha$ -kephalin (IV) by recrystallization from methyl alcohol. Treatment of the sodium salt of compound (III) by hydrazine hydrate leads to the formation of dilinoleoyl- $\alpha$ -kephalin (V), which is purified by chromatography over silicic acid. Distearoyl- $\alpha$ -kephalin (VI) is prepared by treatment of compound (IV) with hydrazine hydrate and purified by reprecipitation from chloroform by means of methyl alcohol. For confirmation of the structure of dilinoleoyl- $\alpha$ -kephalin (V), it was reduced to distearoyl- $\alpha$ -kephalin and identified by comparison with a sample of the latter obtained from  $\alpha, \beta$ -distearoin (II).

The infrared spectrum of dilinoleoyl- $\alpha$ -kephalin has absorption bands similar to the spectrum of dioleoyl- $\alpha$ -lecithin [7] with a strong band at  $975\text{ cm}^{-1}$ , which is characteristic of the covalent phosphorus-oxygen-carbon ( $\text{-POC-}$ ) bond.

### EXPERIMENTAL

Dilinoleoyl-N-phthalimido- $\alpha$ -kephalin (III). 1.9 g of  $\beta$ -dilinoleoin (I) in 10 ml of chloroform and 10 ml of

triethylamine were added, with stirring, to a solution of 1.21 g of the dichloride of  $\beta$ -phthalimidoethylphosphoric acid (m. p. 72-73°) [6] in 4 ml of chloroform at 0°. The reaction mixture was allowed to stand for 48 hours at 15-17°, after which 0.2 ml of water and 0.9 ml of pyridine were slowly added and stirred for two hours at 18-20°. The organic layer was separated and the chloroform removed in vacuo in a current of nitrogen. The residue was dissolved in 90 ml of peroxide-free ether, the insoluble residue removed, washed with 2 N sulfuric acid chilled to 0° (three times, 40 ml each time), then with a saturated aqueous solution of sodium bicarbonate and dried over sodium sulfate. The ether was removed in vacuo. The residue was dissolved in 35 ml of petroleum ether (b.p. 40-60°) and passed through a column (2 x 40 cm) filled with silicic acid. The column was flushed with 110 ml of petroleum ether. The phthalimido- $\alpha$ -kephalin was washed with 50 ml of a mixture of methyl alcohol and ether (1:4). The solvent was driven off in vacuo at 30-35° in a current of nitrogen and the residue dried at 0.1 mm for three hours. The product was a yellow, oily substance that was easily soluble in acetone, chloroform, ether, petroleum ether, the monoethyl ether of ethylene glycol, cyclohexane and benzene; it was slightly soluble in methyl and ethyl alcohol and insoluble in water. The yield was 1.81 g (70.1%).

Found %: C 67.66; H 8.76; N 1.61.  $C_{49}H_{76}O_{10}NP$ . Calculated %: C 67.41; H 8.83; N 1.76.

Dilinoleoyl- $\alpha$ -kephalin (V). During the course of 20 minutes, 4.1 ml of a 0.5 N solution of sodium hydroxide were added, with stirring, to a solution of 1.65 g of compound (III) in 60 ml of the monoethyl ether of ethylene glycol at 5°; then, during a five minute period, 0.072 g of hydrazine hydrate in 0.073 g of water were added. The temperature of the reaction mixture was raised to 60° during the course of an hour and a half and maintained there for one hour. The solvent was removed at 0.8 mm and the residue dried for two hours at 0.1 mm at 30-40°. The product was extracted with warm ether (three times, 25 ml each), filtered and concentrated to 1/3 of the original volume. 1 ml of water, 1 ml of methyl alcohol and 5 g of amberlite IRS-50 (N) were added to the solution and the mixture stirred for 30 minutes. The amberlite was removed, washed with ether and the combined filtrates evaporated. The residue was dried at 0.1 mm for two hours. The solution of kephalin (V) (1.17 g) in 20 ml of chloroform was passed through a column (2 x 50 cm) containing silicic acid. The column was washed with 190 ml of chloroform. The dilinoleoyl- $\alpha$ -kephalin was washed with 300 ml of a mixture of chloroform and methyl alcohol (4:1) and the last 130 ml discarded. The solvent was removed and the residue dried at 0.1 mm for two hours. The product was a faint yellowish, waxy, hygroscopic substance that was easily soluble in chloroform, ether, petroleum ether, methyl and ethyl alcohol, and difficult to dissolve in anhydrous acetone; with water it formed a stable emulsion. The yield was 0.59 g (42.5%).

Found %: C 66.31, 66.62; H 9.90, 10.16; N 1.96, 1.95. Iodine number 135.92, 136.34.  $C_{41}H_{74}O_8NP$ . Calculated %: C 66.60; H 10.01; N 1.90. Iodine number 137.2.

Distearoyl- $\alpha$ -kephalin (VI). 0.05 g of platinum oxide in 10 ml of glacial acetic acid were reduced to platinum black in a current of hydrogen. The acetic acid was decanted and the catalyst washed with glacial acetic acid (three times, 10 ml each). 0.15 g of compound (V) in 10 ml of glacial acetic acid were added to the catalyst and reduction was carried out by means of hydrogen at 18-20° under a 40-50 cm water column. Hydrogenation required 50 minutes and 17.3 ml of hydrogen were absorbed (theoretical: 18.2 ml). The mixture was heated to 40-50°, the catalyst removed, and washed with acetic acid heated to 60° (twice, 15 ml each). The solvent was removed in vacuo at 40-50° and the product dried in a vacuum desiccator over calcium chloride. The yield of crude distearoyl- $\alpha$ -kephalin was 0.15 g. The product was treated with acetone (three times, 10 ml each), separated and dried in vacuo.  $\alpha$ -Kephalin (VI) (0.12 g) was dissolved in 10 ml of chloroform and reprecipitated by 20 ml of methyl alcohol. The precipitate was filtered off, washed with ether and dried in vacuo. The yield was 0.1 g (67.5%). M. p. 180-181°[8].

Found %: N 1.84.  $C_{41}H_{82}O_8NP$ . Calculated %: N 1.88.

Distearoyl-N-phthalimido- $\alpha$ -kephalin (IV). This was prepared from 0.57 g of  $\alpha$ , $\beta$ -distearoin (II) and 0.37 g of the dichloride of  $\beta$ -phthalimidoethylphosphoric acid according to the method described for dilinoleoyl-N-phthalimido- $\alpha$ -kephalin (III). The yield of crude distearoyl-N-phthalimido- $\alpha$ -kephalin was 0.24 g (30.4%). M. p. 47.5-48.5°. After two recrystallizations from methyl alcohol, a colorless crystalline compound was obtained which was easily soluble in chloroform, moderately soluble in ethyl and methyl alcohol, and insoluble in acetone and water. The yield was 0.15 g. M. p. 48.0-48.5°.

Found %: C 67.37; H 9.21; N 1.72.  $C_{49}H_{84}O_{10}NP$ . Calculated %: C 67.23; H 9.59; N 1.60.

Distearoyl- $\alpha$ -kephalin (VI). 0.02 g of hydrazine hydrate were added (to pH 8) to a solution of 0.1 g of compound (IV) in 10 ml of alcohol and boiled for one hour. The hot solution was filtered and acidified with 0.1-0.12 ml of 83% formic acid. On cooling, the  $\alpha$ -kephalin (VI) that was formed separated out along with impurities. The precipitate was filtered off, washed with alcohol and ether and dried in vacuo. It was dissolved in 10 ml of chloroform and the impurities filtered off. The chloroform was removed in vacuo at 40-50°. The residue was dissolved in 8 ml of chloroform and reprecipitated with 16 ml of methyl alcohol. The yield was 0.05 g (49%). M. p. 180.5-181° [8]. A mixed melting point test with distearoyl- $\alpha$ -kephalin, prepared by the reduction of dilinoleoyl- $\alpha$ -kephalin, had a m. p. of 180-181°.

Found %: C 66.07; H 10.97; N 1.95.  $C_{41}H_{82}O_8NP$ . Calculated %: C 65.96; H 10.97; N 1.88.

#### SUMMARY

1. The synthesis of dilinoleoyl- $\alpha$ -kephalin and distearoyl- $\alpha$ -kephalin was achieved.
2. During the course of the synthesis, dilinoleoyl-N-phthalimido- $\alpha$ -kephalin and distearoyl-N-phthalimido- $\alpha$ -kephalin were separated and identified.
3. The structure of dilinoleoyl- $\alpha$ -kephalin was confirmed by reducing it catalytically to distearoyl- $\alpha$ -kephalin.

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SYNTHESIS OF THE METHYL ESTER OF INDOLO-(1,2: 2',3')-3,  
4,5,6,7,8-HEXAHYDROQUINOLIZ-7-YLACETIC ACID

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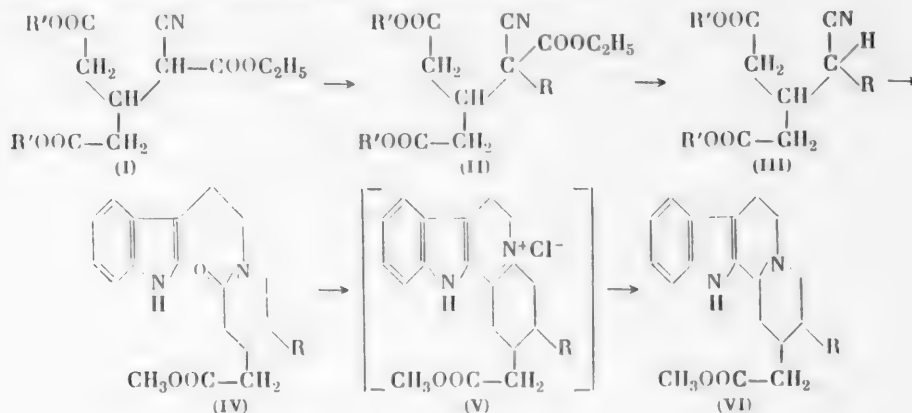
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Our previous investigations showed that esters of  $\beta$ -substituted glutaric acids of the general formula (I) can be used as key substances for the synthesis both of a series of quinoline and isoquinoline alkaloids (emetine [1], C-noremetine [2] and quinine alkaloids [3-5]), and of alkaloids of the pilocarpine group [3].

The present paper describes the synthesis through a series of stages of the methyl ester of indolo-(1,2: 2',3')-3,4,5,6,7,8-hexahydroquinoliz-7-ylacetic acid (VI, R=H). The structure of this compound is the basis of that of corynantheine [6], yohimbine [7] and alkaloids related to them and, with appropriate radicals, may be used for their construction.

The synthesis was carried out according to the following scheme:



Compound (II) was synthesised with the following substituents: R=H,  $CH_2CH_2COOC_4H_9$ ,  $CH_2CH_2N(C_2H_5)_2$  and  $CH_2CH_2N(CH_3)_2$ , which permits the scheme to be used subsequently for producing various derivatives of the indole alkaloids.

The starting materials for the synthesis were the dimethyl and diethyl esters of  $\beta$ -[cyano-(ethoxycarbonyl)-methyl]-glutaric acid (I, R'=CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>), the reaction of which with the butyl ester of  $\beta$ -chloropropionic acid, N-diethylamino- $\beta$ -chloroethane and N-dimethylamino- $\beta$ -chloroethane yielded the  $\beta$ -substituted esters of glutaric acid: the dimethyl ester of  $\beta$ -( $\alpha'$ -ethoxycarbonyl- $\alpha'$ -cyano- $\gamma'$ -butoxycarbonylpropyl)-glutaric acid (II, R=CH<sub>2</sub>CH<sub>2</sub>COOC<sub>4</sub>H<sub>9</sub>, R'=CH<sub>3</sub>), the dimethyl ester of  $\beta$ -( $\alpha'$ -ethoxycarbonyl- $\alpha'$ -cyano- $\gamma'$ -N-diethylaminopropyl)-glutaric acid [II, R=CH<sub>2</sub>CH<sub>2</sub>N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, R'=CH<sub>3</sub>] and the diethyl ester of  $\beta$ -( $\alpha'$ -ethoxycarbonyl- $\alpha'$ -cyano- $\gamma'$ -N-dimethylaminopropyl)-glutaric acid [II, R=CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, R'=C<sub>2</sub>H<sub>5</sub>]. Saponification and decarboxylation of the ester (I, R'=CH<sub>3</sub>) yielded dimethyl ester of  $\beta$ -cyanomethylglutaric acid (III, R=H, R'=CH<sub>3</sub>), and, using this substance as an example, the possibility of creating a heterocyclic system from the esters obtained (II) was shown. The condensation of compound (III, R=H, R'=CH<sub>3</sub>) with tryptamine led to the piperidone (IV), Bischler-Napieral'skii cyclization of which yielded the chloride of the quaternary base (V), and the latter was subjected to reduction in the presence of a Raney nickel catalyst, giving the methyl ester of indolo-(1,2: 2',3')-3,4,5,6,7,8-hexahydroquinoliz-7-ylacetic acid (VI, R=H).

## EXPERIMENTAL

The dimethyl ester of  $\beta$ -cyanomethylglutaric acid [III, R = H, R' = CH<sub>3</sub>] was obtained by selective saponification and decarboxylation of 36 g of the dimethyl ester of  $\beta$ -[cyano-(ethoxycarbonyl)-methyl]-glutaric acid (I, R = CH<sub>3</sub>) [2]. The yield was 15.3 g (69.6%, allowing for 6 g of unsaponified tricarboxylic ester). B. p. 137.5-138° (2.5 mm).

Dimethyl ester of  $\beta$ -( $\alpha'$ -ethoxycarbonyl- $\alpha'$ -cyano- $\gamma'$ -butoxycarbonyl-propyl)-glutaric acid (II, R = CH<sub>2</sub>CH<sub>2</sub>COOC<sub>4</sub>H<sub>9</sub>, R' = CH<sub>3</sub>). To 36 g of the ester (I, R' = CH<sub>3</sub>) and 16 g of potash in 100 ml of acetone, 32 g of the butyl ester of  $\beta$ -chloropropionic acid was added with stirring. The mixture was heated for 18-20 hours on the water bath. The acetone was removed, and the substance was extracted with benzene (3 times with 50 ml portions). The extract was washed with water (30 ml) and dried with sodium sulfate, the benzene was removed and the residue distilled. The yield was 39.6 g (76.6%).

B. p. 175-177° (0.06 mm),  $d_4^{20}$  1.1465,  $n_D^{20}$  1.4640,  $MR_D$  96.15; calculated 96.37.

Found %: C 57.26; H 7.33; N 3.53. C<sub>19</sub>H<sub>29</sub>O<sub>8</sub>N. Calculated %: C 57.13; H 7.31; N 3.50.

Dimethyl ester of  $\beta$ -( $\alpha'$ -ethoxycarbonyl- $\alpha'$ -cyano- $\gamma'$ -N-diethylaminopropyl) glutaric acid [II, R = CH<sub>2</sub>CH<sub>2</sub>N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, R' = CH<sub>3</sub>]. This was obtained in a similar manner to the substance (II, R = CH<sub>2</sub>CH<sub>2</sub>COOC<sub>4</sub>H<sub>9</sub>, R' = CH<sub>3</sub>) from 13 g of the ester (I, R' = CH<sub>3</sub>) and 9 g of N-diethylamino- $\beta$ -chloroethane in the presence of 6 g of potash and 25 ml of acetone. The yield was 8 g (43.4%).

B. p. 150-155° (0.2 mm),  $d_4^{20}$  1.0842,  $n_D^{20}$  1.4668,  $MR_D$  94.60; calculated 94.04.

Found %: C 57.98; H 7.93; N 7.89. C<sub>18</sub>H<sub>30</sub>O<sub>6</sub>N<sub>2</sub>. Calculated %: 58.35; H 8.17; N 7.56.

Diethyl ester of  $\beta$ -( $\alpha'$ -ethoxycarbonyl- $\alpha'$ -cyano- $\gamma'$ -N-dimethylamino-propyl)-glutaric acid [II, R = CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, R' = C<sub>2</sub>H<sub>5</sub>]. To 0.67 g of finely comminuted metallic sodium in 50 ml of xylene, 10.4 g of the diethyl ester of  $\beta$ -[cyano-(ethoxycarbonyl)-methyl]-glutaric acid (I, R' = C<sub>2</sub>H<sub>5</sub>) and 0.2 ml of anhydrous alcohol were added with stirring. The reaction mixture was stirred until the sodium had completely dissolved, after which 12.3 g of N-dimethylamino- $\beta$ -chloroethane was added dropwise and the mixture was heated for a further 4 hours. The mixture was treated with 30 ml of water, the xylene layer was removed, and the aqueous layer was extracted with ether. The combined extracts were treated with 3% hydrochloric acid. The wash waters were neutralized with concentrated ammonia. The oil which separated was extracted with ether (3 times with 20 ml portions) and dried with sodium sulfate. The residue after removal of the solvent was distilled. The yield was 5.7 g [44.3%, or 62.1% taking the recovered initial ester (I) into account].

B. p. 155-162° (1 mm),  $d_4^{20}$  1.081,  $n_D^{20}$  1.4608,  $MR_D$  93.89; calculated 94.04.

Found %: C 58.33; H 8.17; N 7.68. C<sub>18</sub>H<sub>30</sub>O<sub>6</sub>N<sub>2</sub>. Calculated %: C 58.35; H 8.17; N 7.56.

Methyl ester of N-[ $\beta$ -indol-3'-yl]-ethyl]-2-piperid-4-oneacetic acid (IV, R = H). A mixture of 7.9 g of the dimethyl ester of  $\beta$ -cyanomethylglutaric acid (III, R = H) and 9.5 g of tryptamine (m.p. 114-115°) in 30 ml of anhydrous methyl alcohol was hydrogenated in the presence of 1.0 g of a Raney nickel catalyst at 100 atm and 110-115° for 2 hours. The catalyst was removed and the alcohol was distilled off in vacuo. The residue was dissolved in benzene (150 ml) and washed with 3% hydrochloric acid to an acid reaction (pH 3). The aqueous layer was separated, neutralized with potash, and the substance was extracted with chloroform (3 times with 20 ml portions). After distilling off the solvent, the residue was distilled and 3.8-4 g of unreacted tryptamine (b.p. 140-145° at 0.2 mm) was obtained.

The benzene extract was dried with sodium sulfate. The solvent was distilled off and colorless crystals were obtained. The yield was 2.6 g (20.4%).

M.p. 116-117° (from benzene). B.p. 140-145° (0.2 mm). Uv spectrum:  $\lambda_{\text{max}}^{\text{EtOH}}$  228 m $\mu$  (log  $\epsilon$  4.2409), 282 m $\mu$  (log  $\epsilon$  3.7293);  $\lambda_{\text{min}}^{\text{EtOH}}$  245 m $\mu$  (log  $\epsilon$  2.8529).

Found %: C 68.76; H 7.05; N 89.1. C<sub>18</sub>H<sub>22</sub>O<sub>3</sub>N<sub>2</sub>. Calculated %: C 68.79; H 6.98; N 89.94.

Methyl ester of indolo-(1,2: 2',3')-3,4,5,6,7,8-hexahydroquinoliz-7-ylacetic acid (VI, R = H). A solution of 1.9 g of the piperidone (IV, R = H) and 4 ml of phosphorus oxychloride in 30 ml of toluene was boiled for 1 hour. The solvent and the excess of phosphorus oxychloride were distilled off in vacuo. The residue was washed with anhydrous ether (twice, with 25 ml portions), and was then dissolved in 16 ml of 6% hydrochloric acid. The reaction mixture was evaporated in vacuo (5-6 mm) and 3.5 g of an oily substance, reddish-brown in color and soluble in water and al-

cohol, separated. The mass obtained was treated with an alcoholic solution of ammonia (15%) until the reaction was alkaline (pH 10), and the white precipitate of ammonium phosphate which separated was removed. The alcohol was distilled off, the residue (1.6-1.7 g) was dissolved in methanol and hydrogenated in the presence of 1.2 g of a Raney nickel catalyst at 100 atm and 55-60° for 1-1.5 hours. The catalyst was removed, the solvent was distilled off, the residue was washed with aqueous ammonia (pH 10), and the base which separated was extracted with benzene (three times, with 20 ml portions). The solvent was distilled off and colorless crystals, soluble in benzene, alcohol, and ether, and insoluble in water, were obtained. The yield was 1.2 g (81%).

M.p. 125-126° (from ether). Uv spectrum:  $\lambda_{\text{max}}^{\text{EtOH}}$  230 m $\mu$  (log  $\epsilon$  2.620), 282 m $\mu$  (log  $\epsilon$  1.259);  $\lambda_{\text{min}}^{\text{EtOH}}$  245 m $\mu$  (log  $\epsilon$  0.330).

Found %: C 72.15; H 7.29; N 9.60.  $\text{C}_{18}\text{H}_{22}\text{O}_2\text{N}_2$ . Calculated %: C 72.45; H 7.43; N 9.42.

The hydrochloride of the methyl ester of indolo-(1,2: 2',3')-3,4,5,6,7,8-hexahydroquinoliz-7-ylacetic acid (VI, HCl, R=H) is a colorless crystalline substance, soluble in alcohol, less soluble in water, and insoluble in ether and benzene.

M.p. 264-265° (with decomposition in a sealed capillary; from methyl alcohol).

Found %: C 64.73; H 6.58; N 8.25; Cl 10.60.  $\text{C}_{18}\text{H}_{22}\text{O}_2\text{N}_2 \cdot \text{HCl}$ . Calculated %: C 64.75; H 6.64; N 8.39; Cl 10.62.

#### SUMMARY

1. The synthesis of the methyl ester of indolo-(1,2: 2',3')-3,4,5,6,7,8-hexahydroquinoliz-7-ylacetic acid has been carried out through a series of stages.
2. Methods have been developed for obtaining esters of  $\beta$ -substituted glutaric acids: the dimethyl ester of  $\beta$ -cyanomethylglutaric acid, the dimethyl ester of  $\beta$ -( $\alpha'$ -ethoxycarbonyl- $\alpha'$ -cyano- $\gamma'$ -butoxycarbonylpropyl)-glutaric acid, the dimethyl ester of  $\beta$ -( $\alpha'$ -ethoxycarbonyl- $\alpha'$ -cyano- $\gamma'$ -N-diethylaminopropyl)-glutaric acid and the diethyl ester of  $\beta$ -( $\alpha'$ -ethoxycarbonyl- $\alpha'$ -cyano- $\gamma'$ -N-dimethylaminopropyl)-glutaric acid.

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# A NEW SYNTHESIS OF 1,2,4-TRIMETHYL-3,6-HYDROQUINONE

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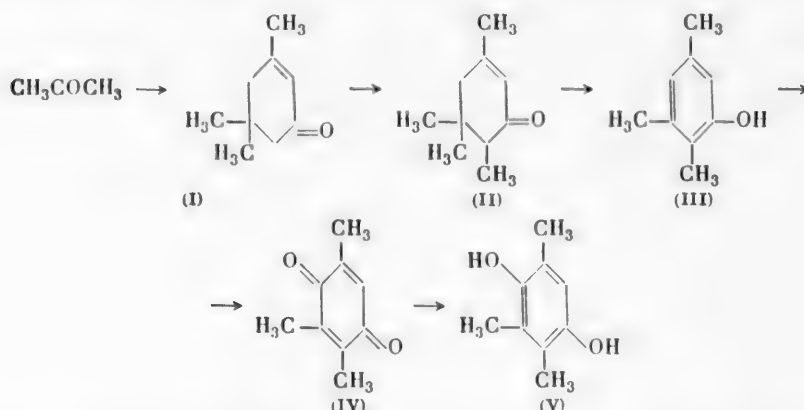
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Vitamin E—5,7,8-trimethyltolcol,  $\alpha$ -tocopherol—performing various functions in the organism, is used in medical practice for the treatment of a number of diseases [1]. The main source of its production is the green parts of plants [2], where it is found mixed with other tococls, the  $\beta$ -,  $\gamma$ -,  $\delta$ -,  $\epsilon$ -,  $\zeta$ -, and  $\eta$ -tocopherols [3], which possess different biological activities [4]. The main methods of synthesizing vitamin E, as a rule, are based on the reaction of 1,2,4-trimethyl-3,6-hydroquinone (V) with natural phytol [5] or isophytol [6] and their derivatives [7]. A number of methods for the production of 1,2,4-trimethyl-3,6-hydroquinone (V) which specify the use of various alkyl-substituted benzenes [8] have been proposed.

The present paper describes a new synthesis of 1,2,4-trimethyl-3,6-hydroquinone (V) based on isophorone (I).



The initial 3,3,5-trimethylcyclohex-5-en-1-one, isophorone (I), obtained by passing acetone vapors through a tube containing calcium oxide, is alkylated with the methyl ester of *p*-toluenesulfonic acid or with dimethyl sulfate, or other methylating agents, to 2,3,3,5-tetramethylcyclohex-5-en-1-one (II). Compound (II) is converted by pyrolysis into 1,2,4-trimethyl-6-hydroxybenzene (III), which is oxidized with potassium nitrosodisulphonate to 1,2,4-trimethyl-3,6-quinone (IV). Reduction of compound (IV) with sodium hydrosulphite gives the corresponding hydroquinone (V).

## EXPERIMENTAL

**Isophorone (I)** With a velocity of 9-10 ml per hour, 108 g of acetone was passed through a steel tube (40 × 800 mm) containing 220 g of granulated calcium oxide and heated in an electric furnace to 375-377°. Unreacted acetone was distilled off from the reaction product, and the residue was distilled. The yield was 10.7 g (62.2% of the acetone that had reacted).

B.p. 102-105° (18 mm),  $d_4^{20}$  0.9095,  $n_D^{20}$  1.4734,  $M_R^{20}$  42.35; calculated for  $C_9H_{14}O$  41.103.

Found %: C 78.12; H 10.00.  $C_9H_{14}O$ . Calculated %: C 78.21; H 10.21.

**2,3,3,5-Tetramethylcyclohex-5-en-1-one (II).** a) A solution of 10 g of isophorone (I) and 27.6 g of piperidine in 100 ml of anhydrous benzene was heated for three hours with the simultaneous removal of the water evolved,

with the help of a water-separator. Then the benzene was distilled off from the reaction mixture, 60 ml of anhydrous methyl alcohol was added and at 0-2°, 40.1 g of methyl iodide was added in the course of 20 minutes. The mixture was heated to boiling for 26 hours, and the excess of methyl iodide and the solvent were distilled off, after which 45 ml of water was added and heating was continued for 2 hours. The reaction product was acidified with 10% sulfuric acid at 15-16° and the substance was extracted with ether (3 times, with 75 ml portions). The combined extracts were washed with 30 ml of saturated aqueous sodium hydrosulphite and dried with sodium sulphate. The residue after the removal of the ether was distilled. The yield was 6.5 g (59.04%).

B.p. 106-107.5° (25 mm),  $d_4^{20}$  0.9200,  $n_D^{20}$  1.4788,  $M_R$  46.89; calculated for  $C_{10}H_{16}OF$  45.72.

Found %: C 78.65; H 10.20.  $C_{10}H_{16}O$ . Calculated %: C 78.96; H 10.59.

b) The reaction was carried out by the method of experiment (a) with the difference that after distilling off the benzene, in place of the methyl iodide 40.4 g of the methyl ester of p-toluenesulfonic acid was added. The yield was 6.1 g (55.4%).

B.p. 102.5-105° (22 mm),  $d_4^{20}$  0.9230,  $n_D^{20}$  1.4790,  $M_R$  46.81. Calculated 45.72.

Found %: C 79.07, 78.88; H 10.20, 10.41.  $C_{10}H_{16}O$ . Calculated %: C 78.96; H 10.59.

c) On methylating compound (I) with dimethyl sulphate under the conditions of the preceding experiments, 2,3,3,5-tetramethylcyclohex-5-en-1-one (II) was obtained with a yield of 30%.

1,2,4-Trimethyl-6-hydroxybenzene (III). With a velocity of 1 ml per minute, 1.7 g of 2,3,3,5-tetramethylcyclohex-5-en-1-one (II) was passed through a quartz furnace heated to 650-675°. The pyrolysis product was collected in an absorber containing a 15% aqueous solution of caustic potash and in a receiver cooled in ice. After the end of the reaction, the apparatus was washed with 150 ml of benzene, which was added to the alkaline solution. The upper, benzene layer was separated, the lower was treated with 10% sulphuric acid, and the substance was extracted with 150 ml of ether. The combined extracts were dried with sodium sulphate. The residue after the removal of the solvent was distilled. The yield was 0.7 g (45.23%). B.p. 112-114° (15 mm).

Found %: C 79.20; H 9.10.  $C_9H_{12}O$ . Calculated %: C 79.43; H 8.90.

1,2,4-Trimethyl-3,6-quinone (IV). To a solution of 0.7 g of 1,2,4-trimethyl-6-hydroxybenzene (III) in 5 ml of ether, a solution of 3.5 g of potassium nitrosodisulphonate in 50 ml of water was added in the course of 1 hour with mechanical stirring. The reaction product was extracted with 150 ml of ether, washed with a 10% aqueous solution of caustic potash (100 ml) and 60 ml of water, and dried with sodium sulphate. To the residue after removal of the ether was added 10 ml of petroleum ether, foreign matter was filtered off, and the solvent removed. The yield was 0.61 g (80.3%). M.p. 50-53°.

1,2,4-Trimethyl-3,6-hydroquinone (V). To a solution of 0.5 g of 1,2,4-trimethylquinone (IV) in 20 ml of benzene was added 1.7 g of sodium hydrosulphite in 15.8 ml of water and the mixture was stirred for 1 hour at 40°. The precipitate which formed was separated off and recrystallized from 1.5 ml of water. The yield was 0.3 g (59.2%). M.p. 168-170°.

Found %: C 71.10; H 7.96.  $C_9H_{12}O_2$ . Calculated %: C 71.27; H 7.95.

#### SUMMARY

A new synthesis of 1,2,4-trimethyl-3,6-hydroquinone has been carried out.

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# A STUDY OF PYRILIUM COMPOUNDS HAVING ACTIVE METHYL GROUPS

## I. THE REACTION OF 2-METHYL-4,6-DIPHENYLPYRILIUM FERRICHLORIDE AND 1,2-DIPHENYLPYRIDINIUM IODIDE WITH BENZALDEHYDE AND p-DIMETHYLAMINO BENZ-ALDEHYDE

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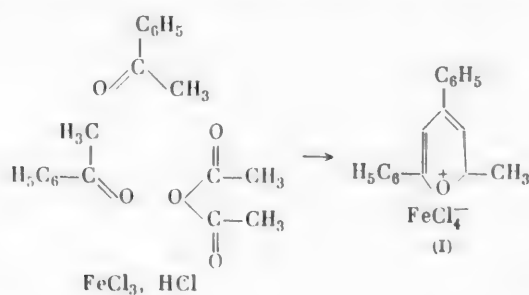
It is known from data in the literature [1] that methyl groups contained in heterocycles and occupying the  $\alpha$ - or  $\gamma$ -position with respect to the hetero atom possess an increased reactivity. It is known that the reactivity is enhanced when the number of hetero atoms in the ring is increased, when the hetero atom is given a positive charge, and also on the introduction of an electronegative substituent into the nucleus. Therefore, there was reason to suppose that on replacing a less electro-negative hetero atom —nitrogen— in the ring by a more electro-negative atom— oxygen — the activity of the methyl group would likewise increase.

The object of the present paper was to investigate whether the activity of the  $\alpha$ -methyl group increased in the transition from a pyridinium compound to a pyriliium compound.

2-Methyl-4,6-diphenylpyriliium ferrichloride, as a representative of the pyriliium series possessing adequate stability, was selected as the object of the investigation. For comparison we synthesized the similarly-constructed 1,2-dimethyl-4,6-diphenylpyridinium iodide.

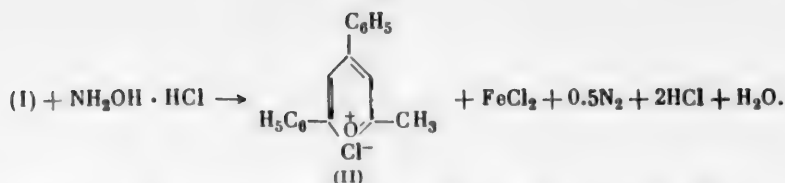
In view of the fact that the synthesis of the substances which were to be used in our work had been inadequately developed, we devised methods of synthesizing some 2-methyl-4,6-diphenylpyriliium and 1,2-dimethyl-4,6-diphenylpyridinium salts.

2-Methyl-4,6-diphenylpyriliium ferrichloride (I) was obtained by a method described in the literature [2] and somewhat modified in our work, from acetophenone, acetic anhydride and ferric chloride, according to the reaction:



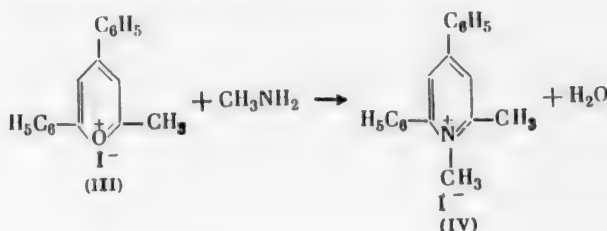
For the transformation to 2-methyl-4,6-diphenylpyriliium chloride (II), we used two methods. In one case, the 2-methyl-4,6-diphenylpyriliium chloride was obtained by treating the corresponding ferrichloride with 10% HCl, and in the second case by treating it with hydroxylamine hydrochloride, which reduces the trivalent iron to bivalent iron according to the equation:





The melting point showed the identity of the product with that obtained earlier [2].

The action of KI on the 2-methyl-4,6-diphenylpyrilium chloride led to the corresponding iodide (III), which, by treatment with methylamine, was converted into 1,2-dimethyl-4,6-diphenylpyridinium iodide (IV).

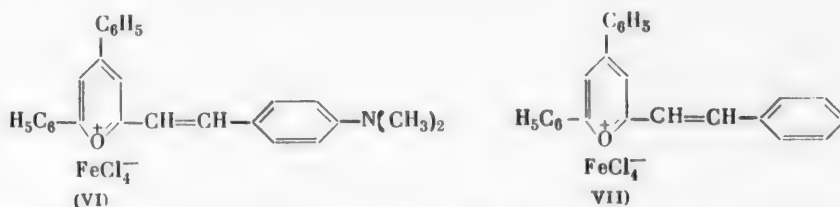


We did not succeed in obtaining pyridinium derivatives from the other 2-methyl-4,6-diphenylpyrilium salts—the chloride and the ferrichloride.

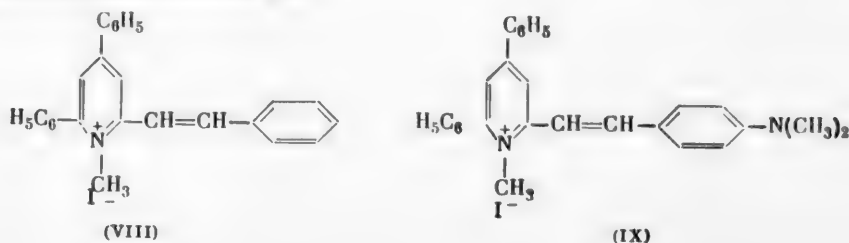
By treating 1,2-dimethyl-4,6-diphenylpyridinium iodide with an aqueous suspension of silver chloride, we obtained 1,2-dimethyl-4,6-diphenylpyridinium chloride (V).

It is known from literature data that 2-methyl-4,6-diphenylpyrilium ferrichloride condenses with benzaldehyde [3]. We found that it also condenses with p-dimethylaminobenzaldehyde. The condensation took place in acetic acid on boiling. Experiments showed that, under these conditions, pyrilium salts give condensation products with aldehydes in good yields, but pyridinium salts do not condense at all.

The product of the condensation of 2-methyl-4,6-diphenylpyrilium ferrichloride with p-dimethylaminobenzaldehyde—2-(p-dimethylaminostyryl)-4,6-diphenylpyrilium ferrichloride (VI)—was obtained by us for the first time, and the product of the condensation with benzaldehyde—2-styryl-4,6-diphenylpyrilium ferrichloride (VII)—has been described [3], the same product being obtained from benzylideneacetone, benzylideneacetophenone and  $\text{FeCl}_3$  in acetic anhydride [4], which confirms the structural formula of this compound.



It is known from the literature that  $\alpha$ -methylpyridine and -pyridinium derivatives condense with aldehydes in alcohol in the presence of piperidine [5]; therefore, we subjected 1,2-dimethyl-4,6-diphenylpyridinium iodide to condensation with benzaldehyde and with p-dimethylaminobenzaldehyde under the indicated conditions and obtained the condensation products—1-methyl-2-styryl-4,6-diphenylpyridinium iodide (VIII) and 1-methyl-2-(p-dimethylaminostyryl)-4,6-diphenylpyridinium iodide (IX).



We also carried out the condensation of 2-methyl-4,6-diphenylpyrilium ferrichloride with p-dimethylamino-benzaldehyde in alcohol in the presence of piperidine and obtained the same product as in the condensation in glacial acetic acid (VI).

We did not succeed in isolating the product of the condensation of 2-methyl-4,6-diphenylpyrilium ferrichloride with benzaldehyde in alcohol in the presence of piperidine, since, under these conditions, apparently, it is unstable.

#### EXPERIMENTAL

**Synthesis of 2-methyl-4,6-diphenylpyrilium ferrichloride (I).** The synthesis was carried out by a modified method described in the literature [2]: 300 g of moist ferric chloride was added to a solution of 300 ml of acetophenone in 1 l of acetic anhydride without cooling. After standing overnight, the precipitate was filtered off and washed with glacial acetic acid. The yield was 83 g. One gram was recrystallized from a mixture of 3 ml of acetic anhydride and 1 ml of glacial acetic acid. M.p. 171-172° (decomp.).

Found %: Cl 32.14, 32.01.  $C_{18}H_{15}OFeCl_4$ . Calculated %: Cl 31.87.

**Synthesis of 2-methyl-4,6-diphenylpyrilium chloride (II).** a) One gram of 2-methyl-4,6-diphenylpyrilium ferrichloride was treated with 30 ml of 10% HCl, and the mixture was stirred for about 1 hour with a mechanical stirrer. Then the yellow precipitate was filtered off and recrystallized from water acidified with HCl, the temperature not rising above 45° on dissolution of the product. After the solution had stood overnight, crystals in the form of golden needles separated. They were filtered off and dried in the vacuum desiccator. Weight 0.2 g. M.p. 123-125° (decomp.).

b) Crude 2-methyl-4,6-diphenylpyrilium ferrichloride (91 g) was added to a solution of 46 g of hydroxylamine hydrochloride in 400 ml of water. The mixture was stirred with a mechanical stirrer at room temperature for 2 hours. The further isolation of the substance was carried out as in the previous experiment. Weight 31 g. M.p. 124-125° (decomp.).

Found %: Cl 11.22, 11.33.  $C_{18}H_{15}OCl \cdot 2H_2O$ . Calculated %: Cl 11.12.

**Synthesis of 2-methyl-4,6-diphenylpyrilium iodide (III).** One gram of 2-methyl-4,6-diphenylpyrilium chloride was suspended in 25 ml of water, and to this suspension a solution of 0.9 g of KI in 18 ml of water was added dropwise with stirring. The addition took 15 minutes, and then the mixture was stirred for a further 5 minutes, and the precipitate was filtered off and washed on the filter with two 0.5 ml portions of water. The precipitate was orange-colored. Weight, after drying in the vacuum desiccator, 1 g. M.p. 200-206° (decomp.). In the literature [6] a m.p. of 204° is given for 2-methyl-4,6-diphenylpyrilium iodide. Hence, we considered it necessary to determine some other constants of the substance obtained—the melting points of mixtures of it with acetanilide and with benzanilide. We found m.p. 97° for the mixture with acetanilide and 147° for the mixture with benzanilide.\* The melting points of the mixtures were determined on the heating bench.

Found %: I 34.71, 34.62.  $C_{18}H_{15}OI$ . Calculated %: I 33.91.

**Synthesis of 1,2-dimethyl-4,6-diphenylpyrilium iodide (IV).** 2-Methyl-4,6-diphenylpyrilium iodide (0.6 g) was added to 25 ml of water, and 10 ml of a 15% solution of methylamine was added dropwise and with vigorous stirring to the suspension obtained. The stirring of the mixture was continued. Soon the orange color of the solution changed to pale brown, and then to greenish grey. After 1 hour a further 5 ml of 15% methylamine was added. The mixture was stirred at room temperature for a further 2.5 hours, and then the precipitate was filtered off and dried in the vacuum desiccator. Weight 0.4 g; after recrystallization from 5 ml of alcohol—0.1 g. On heating in a sealed capillary, it melted at 228-232° (decomp.). On heating on a Böetius heating stage, it melted at 249-250°. A mixture with acetanilide melted at 91°, and a mixture with benzaldehyde at 143°.

Found %: N 3.33, 3.35; I 32.82, 32.61.  $C_{19}H_{18}NI$ . Calculated %: N 3.62; I 32.77.

\* It was necessary to carry out the synthesis of 2-methyl-4,6-diphenylpyridinium iodide under the conditions indicated, since on rapid addition of the KI solution to a suspension of solution of 2-methyl-4,6-diphenylpyrilium chloride products are obtained with a higher content of iodine than 2-methyl-4,6-diphenylpyridinium iodide, reproducibility being lacking.

1,2-Dimethyl-4,6-diphenylpyridinium iodide can be obtained by this method not only from pure 2-methyl-4,6-diphenylpyridinium iodide, but also from products with a high iodine content obtained by the rapid precipitation of a solution or suspension of 2-methyl-4,6-diphenylpyridinium chloride with KI solution.

Synthesis of 1,2-dimethyl-4,6-diphenylpyridinium chloride (V). To a suspension of 1.6 g of 1,2-dimethyl-4,6-diphenylpyridinium iodide in 100 ml of water, freshly prepared AgCl (from 1.5 g of AgNO<sub>3</sub> and 1:1 hydrochloric acid) were added. The mixture was stirred at the boil. The precipitate changed from white to yellow. The mixture was boiled for 7 hours, and then filtered hot. The filtrate was evaporated to dryness, and was dried at a temperature of about 100° and then in the vacuum desiccator. Weight 0.5 g. For purification, the product was dissolved in 1.5 ml of alcohol at the boil, and benzene was added to the solution. After some hours, a precipitate separated which was dried in a vacuum desiccator. Weight 0.3 g. M.p. 217-220° (decomp.).

Found %: Cl 12.36, 12.26. C<sub>19</sub>H<sub>18</sub>NCl. Calculated %: Cl 11.99.

Synthesis of 2-(p-dimethylaminostyryl)-4,6-diphenylpyridinium ferrichloride (VI). A solution of 0.9 g of p-dimethylaminobenzaldehyde in 6 ml of glacial acetic acid was added to a suspension of 2.7 g of 2-methyl-4,6-diphenylpyridinium ferrichloride in 20 ml of glacial acetic acid, and the mixture was boiled for 1 hour. After cooling, the precipitate was filtered off, washed with acetic acid, and dried in a vacuum desiccator. Weight 1.6 g. An amount of 1.1 g of the substance was recrystallized from a mixture of 20 ml of acetic anhydride and 10 ml of glacial acetic acid. Yield 0.86 g. M.p. 212-214° (decomp.). It formed a brownish-violet crystalline powder with a metallic lustre. The solutions had a green color. It is sparingly soluble in water and more soluble in glacial acetic acid and acetic anhydride; it is very soluble in nitromethane. It is practically insoluble in carbon tetrachloride, very sparingly soluble in benzene, and somewhat more soluble in ethyl acetate. It dyes natural silk yellow.

Found %: C 56.09, 56.03; H 4.16, 4.23. C<sub>27</sub>H<sub>24</sub>ONFeCl<sub>4</sub>. Calculated %: C 56.25; H 4.17.

Attempt to condense 1,2-dimethyl-4,6-diphenylpyridinium iodide with p-dimethylaminobenzaldehyde in glacial acetic acid. A mixture of 0.8 g of 1,2-dimethyl-4,6-diphenylpyridinium iodide and 0.3 g of p-dimethylaminobenzaldehyde was boiled for 1 hour in 8 ml of glacial acetic acid. On cooling, 0.62 g of substance separated. After recrystallization from acetic acid, a mixture of it with acetanilide melted at 89° and a mixture with benzanilide at 142°, i.e., the same as the initial product. Repetition of the experiment under the same conditions, but boiling the reaction mixture for 5 hours 40 minutes, gave the same negative results.

Synthesis of 2-styryl-4,6-diphenylpyridinium ferrichloride (VII). One gram of 2-methyl-4,6-diphenylpyridinium ferrichloride dissolved almost completely on boiling with 50 ml of glacial acetic acid. To the boiling solution was added 10 ml of benzaldehyde, and the solution was boiled for 1 hour 45 minutes. At the end of this time, dark red crystals appeared in the solution and the liquid began to bump strongly. The heating was then discontinued. After 2.5 hours, the dark red crystalline precipitate was filtered off. A yield of 0.7 g of 2-styryl-4,6-diphenylpyridinium ferrichloride was obtained. A sample of 0.4 g of the substance was recrystallized from a mixture of 8.5 ml of acetic acid and 8.5 ml of acetic anhydride. M.p. 263-267° (decomp.).\*

Found %: Cl 26.61, 26.66. C<sub>25</sub>H<sub>19</sub>OFeCl<sub>4</sub>. Calculated %: Cl 26.61.

Attempt to condense 1,2-dimethyl-4,6-diphenylpyridinium iodide with benzaldehyde in glacial acetic acid. A solution of 0.9 g of 1,2-dimethyl-4,6-diphenylpyridinium iodide and 10 ml of benzaldehyde in 50 ml of acetic acid was boiled for 1 hour 45 minutes. On cooling, 0.42 g of the initial material separated out. A mixture of it with acetanilide melted at 90° and a mixture with benzanilide at 143°.

Synthesis of 2-(p-dimethylaminostyryl)-4,6-diphenylpyridinium chloride (X). To a solution of 3 g of 2-methyl-4,6-diphenylpyridinium chloride in 50 ml of glacial acetic acid was added a solution of 1.6 g of p-dimethylaminobenzaldehyde in 30 ml of acetic acid. The solution was boiled 4 hours; a green color appeared even at the beginning of the heating. On cooling, no precipitate was formed. By evaporating the solution, a dark grey-green crystalline mass was obtained. It was recrystallized from water on heating to 60°. Fine dark green powder. M.p. 191-194° (in a capillary), 217-221° (on the heating stage). It melted with decomposition.

Found %: Cl 7.49, 7.50. C<sub>27</sub>H<sub>24</sub>ONCl·3H<sub>2</sub>O. Calculated %: Cl 7.58.

It is interesting to note that the aqueous solution of this substance does not give a characteristic precipitate of AgCl with AgNO<sub>3</sub>, but only changes color from dark green to pink and gives a pale brown precipitate.

\* According to data in the literature [3]: m.p. 262°.

**Synthesis of 1-methyl-2-(p-dimethylaminostyryl)-4,6-diphenylpyridinium iodide (IX).** 1,2-Dimethyl-4,6-diphenylpyridinium iodide (0.8 g) was added to 12 ml of alcohol, and then 0.3 g of p-dimethylaminobenzaldehyde and 10 drops of piperidine were also added. The solution was boiled for 7 hours. The color was dark red. On cooling, an oil separated. Ether was added to the mixture. The dark red precipitate which formed was filtered off and dried in the vacuum desiccator. Weight 0.8 g. On heating in a sealed capillary it began to change at about 171°, and melted in the range 176-181° (decomp., from methanol). On heating on the Böetius heating stage, it melted at 175-178°, and then began to crystallize again. This was seen in polarized light. The new crystals melted in the range 188-209°.

Found %: N 5.26, 5.58.  $C_{28}H_{27}N_2I$ . Calculated %: N 5.45.

**Synthesis of 1-methyl-2-styryl-4,6-diphenylpyridinium iodide (VIII).** 1,2-Dimethyl-4,6-diphenylpyridinium iodide (0.8 g) was added to 12 ml of alcohol, and 0.3 ml of benzaldehyde and 10 drops of piperidine were also added. The solution was boiled for 7 hours. On cooling, an oil separated. Subsequently the isolation of a yellow precipitate was carried out in a similar manner to the preceding experiment. Yield 0.8 g. On heating in a sealed capillary, it began to change at 172°. It melted at about 178° (decomp., from methanol).

Found %: N 2.84, 2.85.  $C_{26}H_{22}NI$ . Calculated %: N 2.95.

**Condensation of 2-methyl-4,6-diphenylpyrilium ferrichloride with p-dimethylaminobenzaldehyde in alcohol in the presence of piperidine.** 2-Methyl-4,6-diphenylpyrilium ferrichloride (0.46 g) was added to 6 ml of alcohol and 0.15 g of p-dimethylaminobenzaldehyde and 5 drops of piperidine were also added. On heating, a blue color appeared, the mixture started boiling, and after 30 minutes it began to bump so much that the heating had to be discontinued. After cooling, the color of the solution became brown. A blue precipitate was filtered off, and after drying in the vacuum desiccator it weighed 0.24 g. It dissolved in water with the formation of a blue solution and in glacial acetic acid with the formation of a green solution. The substance was recrystallized from a mixture of 4 ml of acetic anhydride and 2 ml of glacial acetic acid. It formed lustrous brown-violet crystals very similar to 2-(p-dimethylaminostyryl)-4,6-diphenylpyrilium ferrichloride. Weight 0.04 g. M.p. 211-213° (decomp.).

#### SUMMARY

1. It has been shown that 2-methyl-4,6-diphenylpyrilium ferrichloride condenses in glacial acetic acid with p-dimethylaminobenzaldehyde and benzaldehyde forming, respectively, 2-(p-dimethylaminostyryl)-4,6-diphenylpyrilium ferrichloride and 2-styryl-4,6-diphenylpyrilium ferrichloride, while 1,2-dimethyl-4,6-diphenylpyridinium iodide does not react with the aldehydes mentioned under the same conditions.

2. It has been shown that 1,2-dimethyl-4,6-diphenylpyridinium iodide reacts with the aldehydes mentioned in alcohol in the presence of pyridine, forming, respectively, 1-methyl-2-(p-dimethylaminostyryl)-4,6-diphenylpyridinium iodide and 1-methyl-2-styryl-4,6-diphenylpyridinium iodide.

It has been shown that, under these conditions, condensation of 2-methyl-4,6-diphenylpyrilium ferrichloride with p-dimethylaminobenzaldehyde can also be carried out.

3. It has been shown that the activity of the methyl group in 2-methyl-4,6-diphenylpyrilium is higher than in 1,2-dimethyl-4,6-diphenylpyridinium.

4. Six new compounds have been synthesised: 1,2-dimethyl-4,6-diphenylpyridinium iodide and chloride, 2-(p-dimethylaminostyryl)-4,6-diphenylpyrilium ferrichloride, 1-methyl-2-styryl-4,6-diphenylpyridinium iodide, 1-methyl-2-(p-dimethylaminostyryl)-4,6-diphenylpyridinium iodide and 2-(p-dimethylaminostyryl)-4,6-diphenylpyrilium chloride.

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# THE DIENE SYNTHESIS OF ALLOOCIMENE WITH UNSYMMETRICAL DIENOPHILES

## II. SYNTHESIS OF SUBSTITUTED NAPHTHALENES FROM ADDUCTS WITH ALLOOCIMENE

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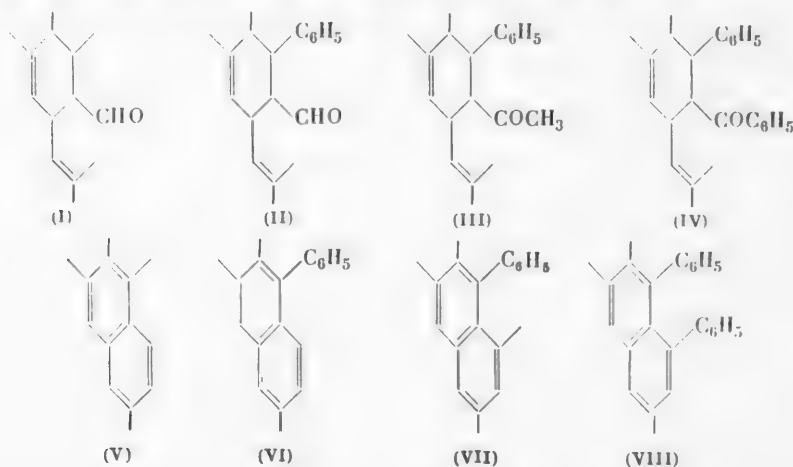
Original article submitted July 9, 1960

As reported earlier [1], when the diene synthesis of alloocimene with unsymmetrical dienophiles is carried out, an isomer of the following structure can be isolated:



In the case where  $X = \text{CHO}$ , dehydrogenation over Pd on carbon with simultaneous dehydration leads to the formation of a naphthalene derivative. Thus, it is easily possible, starting from alloocimene, to synthesize substituted naphthalene derivatives.

In extension of this work, we have obtained adducts of alloocimene with crotonaldehyde—2,3,4-trimethyl-6-(2'-methylprop-1'-en-1'-yl)-1,2,3,6-tetrahydrobenzaldehyde (I); cinnamaldehyde—2-phenyl-3,4-dimethyl-6-(2'-methylprop-1'-en-1'-yl)-1,2,3,6-tetrahydrobenzaldehyde (II); benzylideneacetone—methyl 1-phenyl-2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone (III); and benzylideneacetophenone—phenyl 1-phenyl-2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone (IV)—(see Table 1), and by dehydrogenating them with simultaneous dehydration over Pd on carbon, have isolated the corresponding naphthalene derivatives: 1,2,3,6-tetramethylnaphthalene (V), 2,3,6-trimethyl-1-phenylnaphthalene (VI), 2,3,6,8-tetramethyl-1-phenylnaphthalene (VII) and 2,3,6-trimethyl-1,8-diphenylnaphthalene (VIII) (see Table 2).



As a supplement to the study of the adduct of alloocimene with acrylonitrile, the following ketones were prepared from the latter using Grignard reagents: methyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone (IX), ethyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone (X), n-propyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone (XI), n-butyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone (XII) and phenyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone (XIII) (see Table 3).

TABLE 1. Physical Constants and Analytical Results for Adducts of Alloocimene

Adducts of alloocimene	B. p. (pressure in mm)	M. p.	Empirical formula	% C		% H	
				found	calc.	found	calc.
(I)	112—114° (4)	—	C <sub>14</sub> H <sub>22</sub> O	—	—	—	—
(II)	160—161 (2)	80—81°	C <sub>16</sub> H <sub>24</sub> O	85.25, 85.35	85.03	9.00, 8.95	9.01
(III)	163 (3)	67—69	C <sub>20</sub> H <sub>26</sub> O	85.20, 85.10	85.05	9.70, 9.27	9.28
(IV)	—	134—135	C <sub>28</sub> H <sub>28</sub> O	86.86, 87.00	87.16	8.38, 8.51	8.19

Dehydrogenation of the ketones with simultaneous dehydration over Pd on carbon again led to naphthalene derivatives: 2,3,6,8-tetramethylnaphthalene (XIV), 2,3,6-trimethyl-8-ethylnaphthalene (XV), 2,3,6-trimethyl-8-n-propylnaphthalene (XVI), 2,3,6-trimethyl-8-n-butylnaphthalene (XVII) and 2,3,6-trimethyl-8-phenylnaphthalene (XVIII) (see Table 4).

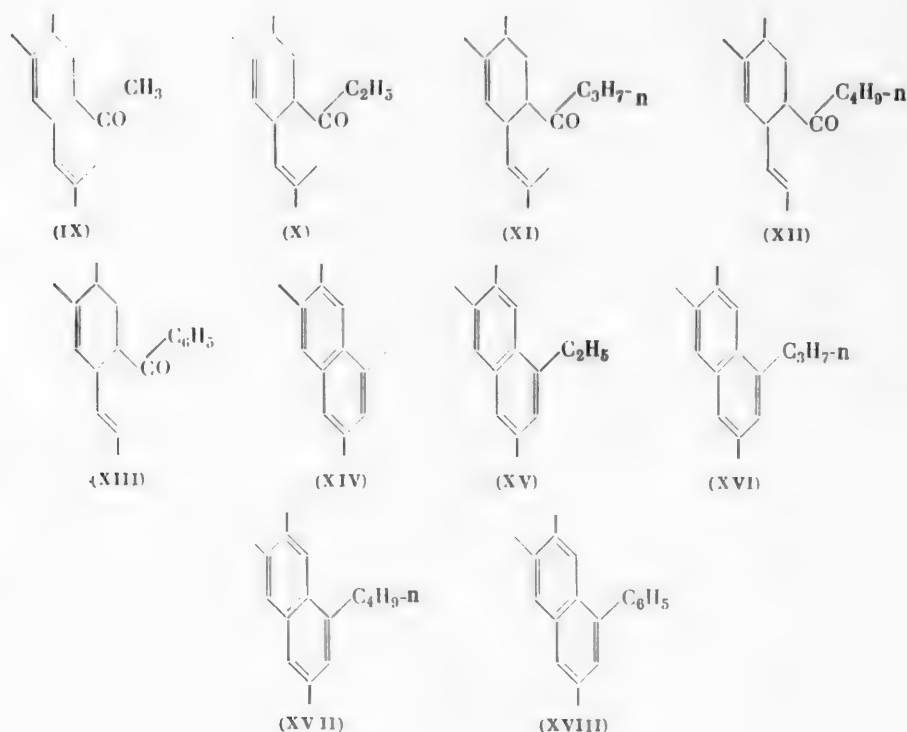




TABLE 2. Melting Points and Analyses of Naphthalene Derivatives

Com- pound	M. p.	Empirical formula	% C		% H		M. p. of the picrate
			found	calc.	found	calc.	
(V)	59–59.5°	C <sub>14</sub> H <sub>16</sub>	91.41, 91.40	91.24	8.58, 8.60	8.75	127.5–128.5° 103–104, unpurified Decomposes be- fore melting Not isolated from solution
(VI)	85–86	C <sub>19</sub> H <sub>18</sub>	92.84, 92.58	92.63	7.39, 7.38	7.36	
(VII)	94–95	C <sub>20</sub> H <sub>20</sub>	92.05, 92.06	92.25	7.81, 7.73	7.74	
(VIII)	162	C <sub>25</sub> H <sub>22</sub>	92.93, 93.10	93.12	6.89, 6.92	6.87	

TABLE 3. Physical Constants and Analytical Data of the Ketones

Com- pound	M. p.	$n_D^{20}$	$d_4^{20}$	$M_R D$		Empirical formula	% C		% H	
				found	calc.		found	calc.	found	calc.
(IX)	102–104° (2.5)	1.4970	0.9270	65.11	63.73	C <sub>14</sub> H <sub>22</sub> O	81.34, 81.25	81.49	10.54, 10.61	10.75
(X)	107–108 (2.5)	1.4845	0.9162	68.78	68.35	C <sub>15</sub> H <sub>24</sub> O	81.11, 81.09	81.76	10.87, 10.92	10.98
(XI)	105.5 (1.5)	1.4838	0.9081	73.76	72.96	C <sub>16</sub> H <sub>26</sub> O	81.53, 81.42	81.97	10.91, 10.86	11.19
(XII)	134 (5)	1.4830	0.9113	77.78	77.58	C <sub>17</sub> H <sub>28</sub> O	81.77, 81.64	82.19	11.34, 11.29	11.37
(XIII)	146–147 (2)	1.5425	0.9956	84.90	83.21	C <sub>19</sub> H <sub>24</sub> O	85.01, 85.25	85.02	8.70, 9.07	9.01

TABLE 4. Melting Points and Analytical Data of the Naphthalene Derivatives

Com- pound	M. p. (from alcohol)	Empirical formula	% C		% H		M. p. of the picrate
			found	calc.	found	calc.	
(XIV)	45–46°	C <sub>14</sub> H <sub>16</sub>	91.42, 91.51	91.24	8.83, 8.90	8.75	127° (from alcohol) 101–103, uncrystallized
(XV)	27–28	C <sub>15</sub> H <sub>18</sub>	91.00, 91.00	90.84	9.30, 9.30	9.15	
(XVI)	59–60	C <sub>16</sub> H <sub>20</sub>	90.90, 90.80	90.49	9.59, 9.60	9.50	82, crude
(XVII)	33–34	C <sub>17</sub> H <sub>22</sub>	89.80, 89.70	90.20	9.80, 9.80	9.80	88, crude
(XVIII)	93	C <sub>19</sub> H <sub>18</sub>	92.57, 92.50	92.63	7.36, 7.48	7.36	106–107, uncrystallized

## EXPERIMENTAL

## Preparation of the Adducts of Alloocimene

1. With crotonaldehyde. The adduct of alloocimene with crotonaldehyde was obtained by B. A. Arbuzov's method [2].

2. With cinnamaldehyde. A mixture of 37 g of cinnamaldehyde, 38.5 g of alloocimene and 0.5 g of hydroquinone was heated in a sealed tube in an oil bath at 160–170° for about 6 hours. After three-times repeated distillation from an Arbuzov flask, a substance in the form of a viscous liquid was isolated from the products; this crystal-

lized after 3 days to form a solid paraffin wax-like mass. The yield was 38 g (50%). The adduct, recrystallized four times from alcohol, had the form of fine threads assembled into stars.

3. With benzylideneacetone. A mixture of 45 g of alloocimene, 48 g of benzylideneacetone and 1 g of hydroquinone was heated in a sealed tube for 5 hours at 200°. Distillation of the reaction products yielded a viscous mass which crystallized after 2 months. On recrystallization from alcohol, the adduct separated from the solvent in the form of conglomerated hairs with no sharp melting point.

4. With benzylideneacetophenone. On heating 24.5 g of benzylideneacetophenone, 16.6 g of alloocimene and 0.5 g of hydroquinone in a sealed tube for 2.5 hours at 180-205°, with subsequent distillation of the reaction products, an adduct was isolated in the form of a pale yellow viscous glass-like mass which crystallized on the addition of methanol. The yield was 23.1 g (71.7%, calculated on the alloocimene which had taken part in the reaction). The adduct, recrystallized repeatedly from methanol and petroleum ether, had the form of very fine needles.

#### Simultaneous Cyclodehydration and Dehydrogenation over Pd on Carbon of the Alloocimene Adducts

1. With crotonaldehyde. A mixture of 7.3 g of the adduct and 5 g of 10% Pd on carbon was heated for 2.5 hours at 220-240°. A yield of 1.7 g of crystalline product was isolated from the reaction mixture; after 3 recrystallizations from alcohol it had the form of very fine lustrous plates.

2. With cinnamaldehyde. A mixture of 1.95 g of the adduct and 1.5 g of Pd on carbon was heated in a Wood's metal bath for 2 hours at 240-250° and for 1 hour at 250-255°. The reaction product was dissolved in petroleum ether (b.p. 40-60°) and transferred to a column of alumina (activity 2-3, according to Brockman). The column was washed with petroleum ether, after evaporation of which a crystalline product was isolated, which, on recrystallization from alcohol, separated in the form of an oil slowly crystallizing on standing. The picrate was not isolated in pure form.

3. With benzylideneacetone. A mixture of 5 g of the adduct in the form of a paraffin wax-like mass and 3 g of palladized carbon was heated in a Wood's metal bath at 230-240° for 1 hour, 240-250° for 1 hour, and at 250-255° for 1.5 hours. The dehydrogenation product was isolated in the form of a very viscous mass which did not crystallize. After purification through the picrate, the product separated from alcohol in the form of an oil solidifying on cooling, and after recrystallization from dry ether it had the form of a white powder. An orange precipitate of the picrate was formed instantaneously on strongly heating the aqueous solutions of the dehydrogenated adduct and picric acid, but its melting point could not be determined since the picrate decomposed before melting.

4. With benzylideneacetophenone. By heating 3.25 g of the adduct of alloocimene with benzylideneacetophenone and 1.8 g of Pd on carbon for 3 hours at 230-240°, 2.9 g of a reaction product in the form of a viscous transparent mass was obtained. By chromatographing this on alumina, a solid product was isolated which crystallized readily from methanol in the form of very fine fibres. No picrate could be isolated from solution.

#### Production of Ketones from Adduct of Alloocimene with Acrylonitrile

1. Production of methyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone. To an ethereal solution of the Grignard reagent obtained from 3 g of magnesium and 40 g of methyl iodide, 12.3 g of the adduct of alloocimene with acrylonitrile was added slowly [1]. The reaction mixture was heated to the boiling point of ether for about 5 hours, was left overnight, and was poured onto finely crushed ice with 50 ml of concentrated hydrochloric acid and boiled under a reflux condenser for 1 hour. By distillation in a column with 27 theoretical plates, 6.7 g (50%) of the ketone in the form of an oily liquid was isolated from the reaction product.

The constants are given in Table 3.

2. The production of ethyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone. To an ethereal solution of the Grignard reagent obtained from 5.15 g of magnesium and 33 g of freshly distilled ethyl iodide, 12.9 g of the adduct of alloocimene with acrylonitrile in ethereal solution was added slowly. The reaction mixture was heated at the boiling point of the ether for about 5 hours, was left overnight, and was poured onto ice with 50 ml of concentrated hydrochloric acid and the mixture was boiled with a reflux condenser for 1 hour. After extraction with ether and removal of the ether from the residue, twice-repeated distillation from an Arbuzov flask yielded the ketone.

3. Production of n-propyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone. To an ethereal solution of the Grignard reagent obtained from 5.1 g of magnesium and 27.1 g of n-propyl bromide was slow-

ly added 9 g of the nitrile in ethereal solution. The reaction mixture was heated to the boiling point of the ether for 2 days and was decomposed by the method described above. After extraction with ether, the ethereal extract was washed with KI solution and pure water and dried over  $\text{Na}_2\text{SO}_4$ , the ether was removed, and from the residue, by twice-repeated distillation from an Arbuzov flask, a colorless, odorless oily liquid was isolated.

4. Production of n-butyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone. To an ethereal solution of the Grignard reagent obtained from 5.2 g of magnesium and 31.4 g of n-butyl bromide was gradually added 8.3 g of the nitrile dissolved in ether, and the reaction mixture was heated for 1.5 days. The reaction product was decomposed with ice and 50 ml of hydrochloric acid, the oily layer was removed, dried and distilled from an Arbuzov flask. A colorless, oily liquid was obtained.

5. Production of phenyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone. To an ethereal solution of phenyl magnesium bromide, prepared from 6.2 g of magnesium and 40.5 g of bromobenzene in 100 ml of ether, 12 g of the nitrile was added slowly with stirring. The mixture was heated for 8 hours and decomposed in the usual way. Distillation from an Arbuzov flask of the resinous mass separated yielded 10.7 g (62.3%) of the ketone in the form of an oily liquid.

#### Cyclodehydration and Dehydrogenation of the Ketones over Pd on Carbon

1. A crystalline product, crystallizing from alcohol in the form of coarse crystals, was isolated by heating methyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone and 2.5 g of palladized carbon at 230-250° for 3 hours. The picrate was three times recrystallized from alcohol (Table 4, compound I).

2. A mixture of 3 g of ethyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone and 2 g of Pd on charcoal was heated in a Wood's metal bath for 1 hour at 220-240° and 1 hour at 240-260°. The reaction product was extracted from the carbon with hot petroleum ether. The residue, after elimination of the ether, was treated with picric acid in alcoholic solution. The picrate which separated was dissolved in dichloroethane, transferred to a column of alumina and eluted with petroleum ether. A crystalline product was isolated. It precipitated from hot alcoholic solution in the form of an oil. It crystallized better in the form of needles on evaporating the solvent in vacuo (Table 4, compound II).

3. A mixture of 5.5 g of n-propyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone and 3 g of Pd on carbon was heated for 2 hours at 230-260°. The reaction product was extracted with ether. The ether was removed, and the residue purified through the picrate by the method described above. A crystalline product in the form of fine crystals crystallizing well was isolated.

4. A mixture of 5.2 g of n-butyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone and 3 g of Pd on carbon was heated for 2 hours at 230-255°. The reaction product, separated from the catalyst, was purified through the picrate with subsequent decomposition of it on alumina. The oil isolated crystallized from alcohol on rubbing with a rod.

5. A mixture of 5 g of phenyl 2,3-dimethyl-5-(2'-methylprop-1'-en-1'-yl)-cyclohex-3-en-6-yl ketone and 3 g of Pd on carbon was heated at 220-225° for 2 hours and at 230-240° for 1 hour 15 minutes. The reaction product had the form of a dense non-friable precipitate.

#### SUMMARY

1. Adducts of alloocimene with cinnamaldehyde, benzylideneacetone and benzylideneacetophenone have been obtained.

2. By dehydrogenating the adducts of alloocimene with crotonaldehyde, cinnamaldehyde, benzylideneacetone and benzylideneacetophenone, with the simultaneous splitting out of water, the corresponding naphthalene derivatives have been obtained.

3. Using Grignard reagents, ketones with methyl, ethyl, n-propyl, n-butyl and phenyl radicals have been obtained from the adduct of alloocimene with acrylonitrile.

4. Simultaneous dehydration and dehydrogenation of the above ketones has yielded the corresponding naphthalene derivatives.

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# THE SYNTHESIS OF ISONICOTINOYLHYDRAZONES OF 2-ACETYL-FURAN AND 2-METHYL-5-ACETYLFURAN

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Synthetic antitubercular preparations, which are derivatives of isonicotinic acid hydrazide, possess one of the leading places in modern medical practice. Of them, only Iarusan\* contains a furan nucleus in the molecule.

We have carried out the synthesis of the isonicotinoylhydrazones of two very stable carbonyl derivatives of furan—2-acetylfuran and 2-methyl-5-acetylfuran. According to foreign advertising announcements [1], the first of them (under the company name of "Menazon") possesses a higher antitubercular activity than the tubazid\* used as the starting point for its synthesis.

The acetylation of furan [2] and sylvan [3] were carried out by the action of acetic anhydride in the presence of orthophosphoric acid on these compounds. The conversion of the 2-acetylfuran and 2-methyl-5-acetylfuran into their isonicotinoylhydrazones was effected by treatment with isonicotinic acid hydrazide.

## EXPERIMENTAL

In a 100 ml flask fitted with a stirrer, thermometer and reflux condenser, were placed 30 ml of methanol, 10 ml of water and 7 g of isonicotinic acid hydrazide (m.p. 169-170°, content of the basic material 98%). The mixture obtained was heated until it formed a homogeneous solution (60-65°) and 5.5 g of freshly-distilled 2-acetylfuran (obtained according to the directions of reference [2] with a yield of 60%, b.p. 64-66° at 13 mm) was added in one portion. The reaction mass was stirred at 60-65° for a further 30 minutes and was left for 35-40 hours to crystallize. The precipitate of 2-acetylfuran isonicotinoylhydrazone was filtered off, washed on the filter with 10 ml of dilute (1:3) methanol, and dried at 60-70° to constant weight. A yield of 9.7 g (85%) of a substance with m.p. 201.5-202.5° (from alcohol) was obtained.

Found %: C 62.82; H 4.96; N 18.07.  $C_{12}H_{11}O_2N_3$ . Calculated %: C 62.88; H 4.80; N 18.33.

2-Acetylfuran isonicotinoylhydrazone is a white crystalline substance, soluble at 20° in 200 parts of water and in 80 parts of alcohol.

2-Methyl-5-acetylfuran isonicotinoylhydrazone was synthesized in a similar way. From 7 g of isonicotinic acid hydrazide and 6.2 g of 2-methyl-5-acetylfuran (obtained in accordance with the instructions of reference [3] with a yield of about 40%, b.p. 68-69° at 7 mm) was obtained 9.75 g (80%) of a substance with m.p. 171.5-172.5°.

2-Methyl-5-acetylfuran isonicotinoylhydrazone is a pale yellow crystalline substance with a slight greenish shade, slightly soluble at 20° in water and alcohol (1:50); it crystallizes from alcohol in the form of fine needles.

Found %: C 64.00; H 5.48; N 17.15.  $C_{13}H_{13}O_2N_3$ . Calculated %: C 64.20; H 5.35; N 17.28.

## SUMMARY

The isonicotinoylhydrazones of 2-acetylfuran and 2-methyl-5-acetylfuran have been synthesized and characterized.

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\* Isonicotinoylhydrazone of 3-(2-furfurylidene)-acetone—Publisher.

\*\* Isonicotinylhydrazine—Publisher.

# INVESTIGATIONS IN THE FIELD OF DIAZO COMPOUNDS

## XIII. THE DIAZOTIZATION OF AROMATIC AMINES WITH NITRITE IN ACETIC ACID AND SUBSTITUTED ACETIC ACIDS\*

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There is only brief information on the possibility of diazotizing amines in carboxylic acid media and on the properties of diazonium salts of these acids [1]. It is most frequently recommended to use acetic, formic, or oxalic acid as the solvent for weakly basic amines, with the obligatory participation in the diazotization of hydrochloric or sulphuric acid [2]. The isomeric nitronaphthylamines [3] and aminoanthraquinones [4] have been smoothly diazotized in acetic acid without mineral acids. The possibility of diazotizing certain *o*-aminoazo compounds [5], and aniline and  $\alpha$ -naphthylamine [6], with nitrite in glacial acetic acid has been mentioned for 1-aminonaphth-2-ol sulphonic acids [7]. Diazotization in concentrated solutions of perhalogenocarboxylic acids has been recommended [8]. Solid diazonium salts with many of these acids have been isolated [9].

It has been established that the diazotization of various amines may be carried out with nitrite in any organic acids, with no participation whatever of mineral acids [10]. Diazotization may be carried out both directly with a suspension of dry nitrite in a solution of the amine in a carboxylic acid, and in a concentrated aqueous solution of nitrite or a solution obtained by the previous low-temperature mixing of dry nitrite with concentrated carboxylic acid. Diazotization takes place both through free nitrous acid and through the nitrosyl carboxylate  $\text{RCOONO}$ . Diazotization proceeds most smoothly and completely in anhydrous or highly concentrated carboxylic acids, which suppress the hydrolysis of the amine salt and ensure the presence of the energetic diazotizing electrophilic agent, the nitrosyl cation  $\text{N}\equiv\text{O}^+$  [11].

TABLE 1

Amine	Yield of diazo compound in percent on the amine after the time (in minutes):			
	5	15	30	60
p-Toluidine	31.9	53.2	68.6	85.1
m-Toluidine	28.9	57.8	75.3	84.6
o-Toluidine	24.3	48.6	56.9	65.3
p-Aminobenzenesulphonic acid	90.1	91.5	100.0	—
m-Aminobenzenesulphonic acid	73.1	85.3	92.7	100.0
p-Aminobenzoic acid	79.1	88.2	100.0	—
o-Aminobenzoic acid	70.5	87.8	100.0	100.0
$\alpha$ -Naphthylamine	50.25	55.3	57.9	62.9
1-Nitro-2-naphthylamine	78.5	84.8	97.9	98.0
4-Nitroaniline-2-sulphonic acid	40.5	47.0	60.9	100.0

\* XIIth communication: ZhOKh 29, 345 (1959).

TABLE 2

Amine	Yield of diazo compound in % on the amine, after the time (in minutes)							
	5		15		30		60	
Aniline	56.4*	5.8**	63.7*	8.4**	66.5*	12.0**	67.3*	17.0**
p-Nitroaniline	89.6	11.6	90.1	11.4	90.3	10.6	90.3	10.6
m-Nitroaniline	89.6	10.2	91.1	11.0	91.5	10.2	91.7	9.6
o-Nitroaniline	60.3	16.7	74.5	15.8	84.9	15.8	90.4	15.55
2,5-Dichloroaniline	71.3	19.6	72.2	22.9	71.6	25.7	71.9	26.7
$\alpha$ -Naphthylamine***	30.3	20.0	33.3	35.0	41.6	42.0	43.1	50.0

\*Diazocompound.

\*\*Diazamino compound.

\*\*\*In place of the diazomino compound, the yields of azo dyes are given.

TABLE 3

Acid	Yield of diazo compound in % on the amine, after the time (in minutes)			
	5	15	30	60
<b>Aniline</b>				
Acetic acid*	12.3	10.6	8.6	—
Monochloroacetic acid	71.3	77.9	93.9	100.0
Trichloroacetic acid	72.9	80.1	96.0	100.0
Hydroxyacetic acid**	44.8	64.1	70.8	72.3
<b>p-Toluidine</b>				
Acetic acid	35.7	48.6	62.2	72.0
Monochloroacetic acid	85.5	93.0	98.7	100.0
Trichloroacetic acid	95.2	97.8	100.0	100.0
Hydroxyacetic acid	48.2	53.8	78.7	82.1
<b>p-Nitroaniline</b>				
Acetic acid***	15.6	18.4	20.7	25.1
Monochloroacetic acid	93.3	97.5	100.0	100.0
Trichloroacetic acid	94.5	98.7	100.0	100.0
Hydroxyacetic acid****	75.1	76.3	77.4	77.6

\*The diazo compound was obtained in addition to the diazomino compound; the yields in percent were, respectively: 71.9, 77.8, 92.66, 93.5.

\*\*The same: 18.34, 6.93, 10.34, 13.84.

\*\*\*The same: 57.2, 58.04, 74.24, 71.3.

\*\*\*\*The same: 6.86, 10.27, 12.1, 11.9.

Our experiments on the diazotization of various monoamines with nitrite in acetic acid and such of its substituted derivatives as monochloro-, trichloro- and hydroxyacetic acids showed the relative ease of carrying out the reaction with formation of diazo compounds. As can be seen from the data of Table 1, in acetic acid such amines as the toluidines, the aminobenzoic acids and the aniline sulphonc acids form 72-100% of diazo compound after only 1 hour. These amines can be diazotized not only in glacial acetic acid, which ensures the fastest reaction, but also in the aqueous acid if 3-4 g-mole of it are used for 1 g-mole of amine. It can be seen from the data of Table 2 that aniline and its chloro and nitro derivatives, in distinction from the weakly basic amines, diazotize with dry nitrite even in glacial acetic acid with the formation not only of the diazo compounds, but also of the diazomino compounds. Of the isomeric nitroanilines, o-nitroaniline has the greatest tendency to form diazomino compounds in glacial acetic acid. In aqueous acetic acid, using 4 g-mole of it for 1 g-mole of amine (2.4% of acid), the formation of diazo-



amino compounds from such amines becomes predominating. The diazotization of  $\alpha$ -naphthylamine is complicated by the comparatively rapid combination of part of the diazo compound with unchanged amine to form an azo dye.

TABLE 4

Double salt	% Hg		Diazo N, %		Crystal characteristics (needles)	Ignition tem- perature
	found	calc.	found	calc.		
Acetic acid salts						
$C_6H_5-N_2-OCOCH_3 \cdot HgCl_2$	46.29	46.06	6.71	6.43	yellow-orange	119-121°
$p-CH_3-C_6H_4-N_2-OCOCH_3 \cdot HgCl_2$	45.1	44.64	6.23	6.22	colorless	159-161
$p-O_2N-C_6H_4-N_2-OCOCH_3 \cdot HgCl_2$ *	41.18	41.75	5.82	5.83	orange	142-143
$o-HOOC-C_6H_4-N_2-OCOCH_3 \cdot HgCl_2$	42.64	41.83	5.84	5.98	pale brown	106-107
$p-HOOC-C_6H_4-N_2-OCOCH_3 \cdot HgCl_2$	42.19	41.83	5.63	5.98	pale brown	79-80
$\alpha-C_{10}H_7-N_2-OCOCH_3 \cdot HgCl_2$	41.52	41.34	5.98	5.77	brown	92-93
$1,2-O_2N-C_{10}H_6-N_2-OCOCH_3 \cdot HgCl_2$	38.7	37.81	5.18	5.28	yellow	121-122
Monochloroacetic acid salts						
$C_6H_5-N_2-OCOCH_2Cl \cdot HgCl_2$	42.38	42.68	5.58	5.96	cream	103-105
$p-CH_3-C_6H_4-N_2-OCOCH_2Cl \cdot HgCl_2$	41.54	41.67	5.65	5.78	colorless	131-133
$p-O_2N-C_6H_4-N_2-OCOCH_2Cl \cdot HgCl_2$	38.91	38.95	5.16	5.44	pale yellow	122-125
Trichloroacetic acid salts						
$C_6H_5-N_2-OCOCCL_3 \cdot HgCl_2$ **	37.43	37.22	5.19	5.34	colorless	126-128
$p-CH_3-C_6H_4-N_2-OCOCCL_3 \cdot HgCl_2$	36.28	36.28	5.06	5.12	colorless	142-144
$p-O_2N-C_6H_4-N_2-OCOCCL_3 \cdot HgCl_2$	34.41	34.35	4.79	4.96	pale yellow	134-136

\* Found %: Cl 14.25. Calculated %: 14.79.

\*\* Plates.

In accordance with their capacity for forming diazo compounds with maximum yields on diazotization in concentrated acetic acid for 15-30 minutes, the amines may be arranged in the following decreasing order:  $p$ -nitroaniline >  $m$ -nitroaniline >  $p$ -anilinesulphonic acid >  $p$ -aminobenzoic acid >  $o$ -aminobenzoic acid > 1-nitro-2-naphthylamine >  $m$ -anilinesulphonic acid > aniline >  $o$ -nitroaniline > 2,5-dichloroaniline >  $p$ -toluidine >  $m$ -toluidine >  $o$ -toluidine >  $\alpha$ -naphthylamine >  $\beta$ -naphthylamine. Thus, just as was noted earlier for mineral acids [12], the rate of diazotization of amines with nitrite in acetic acid rises with the introduction into the nucleus of electrophilic substituents in the order:  $NO_2 > SO_3OH > COOH > Cl$ . The rate of diazotization diminishes with the introduction of electron-donating substituents. The influence of substituents present in the para position is greater than those in the ortho and meta positions.

On comparing the results of diazotization with nitrite in aqueous solutions of acetic acid and its substituted derivatives, it may be noted that the rate of diazotization of amines different in nature - aniline,  $p$ -toluidine and  $p$ -nitroaniline - is in complete agreement with the constants of electrolytic dissociation of the carboxylic acids taken [13] (Table 3): trichloroacetic > monochloroacetic > glycolic > acetic acid. The diazotization of aniline and  $p$ -nitroaniline in such strong acids as the chloroacetic acids takes place without the formation of diazoamino compounds. The ease of formation of diazoamino compounds for acetic and glycolic acids is connected with the considerable reversibility of the reaction of salt formation of aniline and the nitroanilines in weak carboxylic acids.

A number of diazonium salts of carboxylic acids were isolated in the form of double salts with mercuric chloride (Table 4). The action of the light of a 500 w electric lamp at 20°, and also storage in a closed vessel in the dark at the same temperature, on solutions of the diazo compounds showed that the stability of the diazonium salts of carboxylic acids can be expressed in the following decreasing series: diazonium trichloroacetate > monochloroacetate > chloride > acetate > glycolate.

TABLE 5

Diazonium salt	Decomposition of the diazo compound, % of initial time of irradiation with 500 W lamp, hr							
	0.5		1.0		2.0		3.0	
	light	dark- ness	light	dark- ness	light	dark- ness	light	dark- ness
<b>Benzenediazonium salts:</b>								
Acetate	26.3	16.7	44.7	27.8	73.7	50.0	99.0	61.1
Monochloroacetate	7.0	4.7	14.0	7.0	23.3	14.0	30.2	18.6
Trichloroacetate	6.5	4.3	8.7	10.9	21.75	15.2	28.3	21.7
Hydroxyacetate	6.4	4.3	14.9	10.6	21.3	17.0	38.0	23.4
Chloride	18.6	9.3	32.6	20.9	41.85	35.0	60.5	44.2
<b>p-Toluenediazonium salts:</b>								
Acetate	11.7	7.0	23.3	16.4	39.4	34.8	60.4	55.7
Monochloroacetate	10.3	8.6	18.9	12.9	35.8	23.8	48.6	36.1
Trichloroacetate	8.1	4.3	23.1	10.7	29.5	11.4	40.1	29.9
Hydroxyacetate	15.7	9.1	26.8	22.4	39.9	35.5	60.0	53.3
Chloride	16.7	8.6	21.0	15.0	40.2	25.7	57.2	42.4
<b>p-Nitrobenzenediazonium salts:</b>								
Acetate	15.8	11.0	31.7	19.9	42.9	35.4	58.7	44.2
Monochloroacetate	14.5	6.2	26.9	20.7	37.3	31.1	49.7	41.4
Trichloroacetate	10.4	4.1	22.7	16.5	31.1	22.7	43.5	33.2
Hydroxyacetate	17.3	12.7	32.5	23.3	47.5	38.1	64.7	46.5
Chloride	18.6	6.2	32.6	20.6	41.6	26.9	57.95	37.3

For aniline, the stability of the diazonium glycolate is higher than that of the acetate. The stability of the diazonium trichloroacetates is 2 to 3 times higher than the stability of the diazonium chlorides. The rate of decomposition of the diazo compounds is twice as high on irradiation as in the dark. Just as was known for mineral acid diazonium salts [14], light most strongly affects the diazonium salts of carboxylic acids derived from those amines which contain electrophilic groups in the molecule (Table 5).

#### EXPERIMENTAL

**Diazotization.** The pure amine (0.01 g-mole) was dissolved without heating in 100 ml of glacial acetic acid, the solution was cooled to 0-5° and 0.011 g-mole of dry ground sodium nitrite was added with stirring. On diazotizing in aqueous solutions of carboxylic acids, 0.01 g-mole of the amine was dissolved in 90 ml of the acid (0.04-0.12 g-mole) with slight warming, and the solution was then rapidly cooled to 0-5°. In some cases, this led to the separation of a microcrystalline precipitate of the amine salt. To the solution or fine suspension of the amine salt obtained, 0.011 g-mole of nitrite in 10 ml of water was rapidly added, and the mixture was maintained for a predetermined time at 0-5°. The reaction was interrupted by the addition of dry sulphuric acid amide, and the amount of diazo compound formed was determined: by decomposition in a sulfuric acid solution of dichromate at the boil, with collection of the diazo nitrogen, and, parallel with this, by combination with a 0.1 N solution of  $\beta$ -naphthol, with subsequent titration of the excess of the latter with a p-nitrobenzene diazonium solution. By doubling the result obtained on subtracting the percentage yield of diazo compound according to the yield of azo compound from the percentage yield according to the diazo nitrogen, the percentage yield of diazoamino compound is found. As a check, for some amines the yield of diazoamino compound was determined by a gravimetric method, the compound being isolated from the reaction solution. The experimental figures in the tables are the means of three parallel experiments.

**Isolation of the diazoamino compounds in the diazotization of some amines.** a) A solution of 9.3 g (0.1 g-mole) of pure aniline in 100 ml of a 4 M solution of acetic acid was cooled to 0-5°, and a solution of 7.1 g of nitrite in 20 ml of water was added. The mixture was kept for 30 minutes in the cold and 500 ml of water was added. The orange-yellow crystalline precipitate which separated was filtered off, washed with cold water, and dried in the vacuum desiccator over caustic potash. A yield of 9.1 g (92.4%) of a substance with m.p. 98° (from aqueous alcohol) was obtained [15].

b) Under similar conditions, 13.8 g (0.1 g-mole) of p-nitroaniline yielded 14 g (97%) with m.p. 234° (from benzene), which corresponds to 4,4'-dinitrodiazoaminobenzene [16].

Isolation of the dye on diazotizing  $\alpha$ -naphthylamine. A solution of 1.43 g of  $\alpha$ -naphthylamine (0.01 g-mole) in 2.4 ml of glacial acetic acid (0.04 g-mole) was made up to 100 ml with water, cooled to 0°, and diazotized with a nitrite solution. After 1 hour of vigorous stirring, the solution was rapidly poured into a cooled aqueous solution of caustic soda. The precipitate which separated was filtered off, washed with cold, and then with hot, water, and dried and weighed. A yield of 0.744 g (51 %) of a dye in the form of dark red needles with m.p. 173-175° (from a mixture of alcohol and ether) was obtained; this corresponds to  $\alpha$ -naphthylazonaphthylamine [17].

The isolation of double salts of diazo compounds with mercuric chloride. To an aqueous solution of a diazo compound, with external cooling and stirring, was added a 10% solution of mercuric chloride in an amount equivalent to the amine. The diazo solutions obtained in concentrated carboxylic acids were diluted 3- to 4-fold with water before the addition of the mercuric chloride. The heavy crystalline precipitate which separated was filtered off, washed with ice water and then with cold alcohol, and dried in a vacuum desiccator over caustic potash in the dark. The yield of double salts of the diazonium salts of carboxylic acids with mercuric chloride amounted to 90-98% (Table 4).

Determination of the stability of the diazo solutions with time on irradiation and on storage in the dark. The amine (0.01 g-mole) was diazotized with nitrite in carboxylic acid solution as above. The excess of nitrite was decomposed with urea. Where diazoamino compounds were formed, these were previously filtered off and the clear solution used for the experiment. A 10 ml sample of the diazo solution—before and after the time experiment—was mixed with an excess of methylphenylpyrazolonesulphonic acid in bicarbonate solution, and after 30 minutes the mixture was acidified with hydrochloric acid and the excess of the azo component was titrated with nitrite solution. Irradiation of the solutions of the diazo compounds in plane cells was carried out with a 500 w lamp placed behind protective glass at a distance of 1 m from the solutions.

#### SUMMARY

1. The diazotization of amines with nitrite in acetic, glycolic and chloroacetic acids has been studied. The greatest effect on the diazotization is connected with the high electrical dissociation constants of these acids.
2. A series of diazonium salts of carboxylic acids has been isolated as solids in the form of double salts with mercuric chloride.
3. The stability of aqueous solutions of diazonium salts of acetic acid and its substituted derivatives to the action of light and storage in the dark has been established.

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## INVESTIGATIONS IN THE FIELD OF DIAZO COMPOUNDS

### XIV. THE DIAZOTIZATION OF AROMATIC AMINES WITH NITRITE IN SATURATED CARBOXYLIC ACIDS\*

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Having established the possibility of diazotizing amines with nitrite in carboxylic acids completely without the participation of mineral acids [1], we have studied in more detail the diazotization of a series of amines in monobasic and dibasic saturated carboxylic acids.

In the literature there is reference only to particular cases of the use of individual carboxylic acids (acetic, oxalic [2], and formic) for the diazotization of certain amines. In relation to formic acid, the information is inconsistent: thus, it is indicated that it cannot be used in view of its ready oxidation by the action of the nitrite [3], while it is recommended to diazotize 1,4,5,8-tetraaminoanthraquinone and the like in formic acid [4].

The diazotization of amines with the vigorous diazotizing agents, the nitrosyl carboxylates, was carried out by the addition of dry sodium nitrite to a solution of the amine in an excess of concentrated carboxylic acid (propionic, n-butyric, 80% formic) at 0-5°, or in a 1,8-4,0 N aqueous solution of the acid (4 g-mole per 1 g-mole of amine) (Tables 1 and 2).

On comparing the yields of diazo compounds for the same amines in saturated carboxylic acid, a dependence of the rate of diazotization on the value of the dissociation constant of these acids was observed, the rate decreasing in the sequence: oxalic and formic > malonic > succinic > acetic > n-butyric > propionic acid.

Some exception to this general relation between the rates of diazotization and the dissociation constants for formic and monochloroacetic acid is probably connected with the fact that in these cases the specific structure of formic acid and the influence of the chlorine atom in chloroacetic acid has great importance. It must also be pointed out that, in contrast to all other carboxylic acids, formic and monochloroacetic acids have low dielectric constants. Many amines diazotize perfectly smoothly in anhydrous n-butyric and propionic acids.

According to their capacity for diazotization in formic acid with maximum yields, the amines can be arranged in the following decreasing sequence: p-nitroaniline > p-anilinesulphonic acid > p-toluidine > o-toluidine > p-aminobenzoic acid > o-aminobenzoic acid >  $\alpha$ -naphthylamine.

If the amount of carboxylic acid used (from 4 g-mole and above) and its basicity are not taken into account, the capacity of certain amines, for example para-substituted amines, for maximum diazotization in all saturated carboxylic acids rises with the presence in the nucleus of substituents in the following sequence:  $\text{NO}_2 > \text{SO}_2\text{OH} > \text{COOH} > \text{CH}_3$ .

The diazotization of aniline and such weakly basic amines as the nitroanilines and 2,5-dichloroaniline in aqueous solutions of carboxylic acids is complicated by the formation of considerable amounts of the diazoamino compounds (Table 3). The lower the electrolytic dissociation constant of the carboxylic acid, the greater is the tendency of these amines to form diazoamino compounds. For many amines, an increase in the concentration of these acids considerably reduces the amount of diazoamino compound formed. Thus, for example, while p-toluidine diazotizes with the formation of considerable amounts of the diazoamino compound in aqueous butyric acid (4 g-mole), in concentrated butyric acid none of the latter is formed at all. However, where such weak acids as propionic are used, even at 100% concentration, the diazotization of aniline and weakly basic amines leads to the formation both of the diazo

\* XIIIth Communication: ZhOKh 31, 2206 (1961).

TABLE 1

Amine	Yield of diazo compound in % of the amine			
	time, min			
	5	15	30	60
Formic acid (0.04 g-mole)				
p-Toluidine	81.3	87.6	98.1	100.0
o-Toluidine	73.5	77.6	85.3	89.6
p-Anilinesulphonic acid	82.7	93.8	100.0	—
p-Aminobenzoic acid	56.8	73.8	89.8	100.0
o-Aminobenzoic acid	47.8	53.6	61.1	88.3
$\alpha$ -Naphthylamine	36.5	41.8	50.1	63.3
p-Nitroaniline	95.6	95.6	98.1	98.7
p-Toluidine*	84.3	93.5	98.7	100.0
Aniline*	67.2	79.1	100.0	100.0
p-Nitroaniline*	95.1	97.6	99.8	100.0
100% n-Butyric acid				
p-Toluidine	39.9	44.6	61.3	71.7
p-Nitroaniline	63.1	70.1	71.7	72.3
p-Aminobenzoic acid	43.6	62.7	84.3	100.0
$\alpha$ -Aminoanthraquinone	21.6	43.7	71.6	81.4
100% Propionic acid				
p-Toluidine	39.1	43.6	52.3	65.6
p-Aminobenzoic acid	42.7	68.4	75.2	80.4

\*Diazotization in 80% formic acid.

TABLE 2

Amine	Yield of diazo compound in % of the amine			
	time, min			
	5	15	30	60
Oxalic acid (0.04 g-mole)				
p-Toluidine	74.6	80.7	88.1	96.8
p-Anilinesulphonic acid	86.4	92.1	100.0	100.0
p-Aminobenzoic acid	61.7	75.8	93.1	100.0
$\alpha$ -Naphthylamine	33.0	49.6	61.0	72.3
p-Nitroaniline	74.6	80.7	91.0	91.3
Aniline*	59.3	78.6	87.7	93.8
Succinic acid (0.04 g-mole)				
p-Toluidine	55.1	62.6	70.3	78.8
p-Nitroaniline	84.3	87.2	93.7	100.0
Malonic acid (0.04 g-mole)				
p-Toluidine	67.8	84.2	86.7	93.1

\*Diazotization with 0.12 g-mole of oxalic acid.

TABLE 3

Amine	Yield of diazo compound, %							
	after the time, min:							
	5		15		30		60	
	diazo	diazo-amine	diazo	diazo-amine	diazo	diazo-amine	diazo	diazo-amine
Formic acid (0.04 g-mole)								
Aniline	58.6	40.3	68.1	14.0	71.5	26.0	82.6	24.0
2,5-Dichloroaniline	16.4	49.0	14.2	68.4	14.0	78.8	13.6	82.1
Propionic acid (0.04 g-mole)								
Aniline	10.3	72.6	8.7	83.2	6.3	93.1	—	—
2,5-Dichloroaniline	6.4	48.8	5.5	56.9	5.6	77.1	5.0	84.9
p-Nitroaniline	6.4	52.1	8.3	68.3	11.6	73.3	12.1	87.3
p-Toluidine	33.1	1.9	34.7	3.6	64.7	4.4	71.6	8.6
Aniline*	39.4	16.4	42.6	24.7	45.0	37.9	50.6	49.0
p-Nitroaniline*	35.6	40.3	48.1	25.2	53.7	36.1	53.7	36.9
n-Butyric acid (0.04 g-mole)								
p-Nitroaniline	7.3	53.6	9.6	66.4	13.8	70.6	17.1	75.7
Aniline*	30.1	0.9	35.6	8.1	58.4	32.6	68.3	31.0
Malonic acid (0.04 g-mole)								
Aniline	42.6	17.4	54.6	29.0	57.1	32.3	60.3	34.2
p-Nitroaniline	70.3	7.4	71.4	17.5	77.6	19.2	79.6	21.5
Oxalic acid (0.04 g-mole)								
Aniline	53.3	5.9	68.4	9.9	69.1	10.2	74.1	93.8
2,5-Dichloroaniline	18.4	33.3	22.3	35.0	34.6	42.5	42.1	58.4
Succinic acid (0.04 g-mole)								
Aniline	36.7	11.1	41.6	23.0	52.4	19.0	60.3	22.4

\*Diazotization in 100% acid.

compound and of considerable amounts of the diazoamino compound. In aqueous propionic acid, using 4 g-mole of it per 1 g-mole of amine, even p-toluidine forms a small amount of the diazoamino compound (8.5% after 1 hour) in addition to a considerable amount of the diazo compound (72% in 1 hour). This amine forms no diazoamino compound at all in aqueous solutions of other carboxylic acids. The diazotization of  $\alpha$ -naphthylamine in concentrated propionic acid is complicated by the formation of an azo dye, as has been recorded for this amine also when it is diazotized in concentrated acetic acid [1]. 2,5-Dichloroaniline possesses the greatest capacity for the formation of diazoamino compounds in carboxylic acids of various concentrations. The diazoamino compounds from this amine also form in aqueous solutions of such strong acids as formic and oxalic. Aniline is capable of diazotizing smoothly without the formation of diazoamino compounds in these acids only at high concentrations of them in water. While p-nitroaniline diazotizes smoothly in concentrated n-butyric acid to the extent of 71% after 30 minutes, in an aqueous solution of this acid it gives the same yield, but of the diazoamino compound, and only a 14% yield of the diazo compound.

A number of diazonium salts of carboxylic acids were isolated in the form of their double salts with mercuric chloride (Table 4). The action of the light of a 500 w electric lamp on aqueous solutions of the diazo compounds, and also the storage of the solutions in closed vessels in the dark (Table 5), showed that the stability of solutions of diazo compounds agrees with the position of the carboxylic acids in the homologous series. The higher the carboxy-



TABLE 4

Double salt	% Hg		Diaz. N, %		Crystal characteristics	Ignition temperature
	found	calc.	found	calc.		
Formates						
$C_6H_5-N_2-OCOH \cdot HgCl_2$ *	49.13	49.2	6.94	6.87	Pink plates	99°
$p-CH_3-C_6H_4-N_2-OCOH \cdot HgCl_2$	47.31	47.58	6.83	6.64	Large colorless needles	121—122
$p-O_2N-C_6H_4-N_2-OCOH \cdot HgCl_2$	45.01	44.82	6.42	6.25	Very fine pale yellow plates	127—128
$p-HOOC-C_6H_4-N_2-OCOH \cdot HgCl_2$	45.13	44.99	6.38	6.27	Fine colorless plates	98—99
$\alpha-C_{10}H_7-N_2-OCOH \cdot HgCl_2$	42.47	42.54	5.98	5.94	Pale brown plates	101—102
$1,2-O_2N-C_{10}H_6-N_2-OCOH \cdot HgCl_2$	39.12	38.83	5.84	5.42	Yellow plates	117—118
Oxalates						
$C_6H_5-N_2-HC_2O_4 \cdot HgCl_2$	43.21	43.07	5.87	6.01	Long white needles	102
$p-CH_3-C_6H_4-N_2-HC_2O_4 \cdot HgCl_2$ **	41.36	41.82	5.92	5.84	Long white needles	142
$p-O_2N-C_6H_4-N_2-HC_2O_4 \cdot HgCl_2$	39.26	39.28	5.74	5.48	Conglomerates of fine white needles	143—144
$p-HOOC-C_6H_4-N_2-HC_2O_4 \cdot HgCl_2$	39.14	39.37	5.84	5.49	Long white needles	106—107
$\alpha-C_{10}H_7-N_2-HC_2O_4 \cdot HgCl_2$	39.21	38.94	5.61	5.43	Fine yellow needles	109—111

\* Found %: Cl 16.45. Calculated %: Cl 16.86.

\*\* Found %: Cl 14.68. Calculated %: Cl 14.82.

lic acid homologue, the less stable are the diazonium salts which it forms. The diazonium salts of formic acid exhibit the greatest stability and those of oxalic the least. The stability of diazonium salts with saturated monocarboxylic acids is lower than that of the diazonium salts of hydrochloric acid and those of dibasic saturated carboxylic acids. Such dibasic carboxylic acids as oxalic and succinic impart the greatest stability to the diazo compounds. Aniline and p-nitroaniline form more stable diazonium salts with oxalic acid than with hydrochloric acid. Malonic acid forms extremely unstable diazonium salts. On storing a diazonium salt of malonic acid in the dark and, particularly, on irradiating it in the reaction solution, a quite rapid formation of orange-red precipitates is observed. The latter consist of the products of a far-reaching conversion of the diazo compound with the excess of malonic acid in the solution [5]. Solutions of the diazo compounds in glacial acetic acid are more stable (1.5-2 times) than in aqueous solutions of this acid. The differences in the stability of diazo compounds in concentrated (80%) and aqueous formic acid are inconsiderable.

#### EXPERIMENTAL

**Diazotization.** The amine (0.01 g-mole) was dissolved without heating in 100 ml of concentrated acid (n-butyric, propionic, or 80% formic). To the solution, cooled to 0-5°, was added 0.011 g-mole of dry sodium nitrite, with stirring. In other respects the procedure was similar to that described for acetic acid [1].

**Isolation of the diazoamino compounds.** A solution of 16.2 g (0.1 g-mole) of 2,5-dichloroaniline in 100 ml of 4 M formic acid was cooled to 0-5° and an aqueous solution of sodium nitrite was added. The mixture was kept in the cold for 30 minutes, and 500 ml of water was added. The yellow flocculent precipitate which separated was filtered off, washed with cold water, and dried in the vacuum desiccator over caustic potash. The yield was 13.4 g (80%) of a substance with m.p. 171° (from benzene), which corresponds to 2,2',5,5'-tetrachlorodiazoaminobenzene [6].

TABLE 5

Diazonium salt	Decomposition of diazo compound, % of initial							
	time of irradiation with 500 w lamp, hr							
	0.5		1.0		2.0		3.0	
	in light	in dark	in light	in dark	in light	in dark	in light	in dark
<b>Benzenediazonium salts:</b>								
Chloride	18.6	9.3	32.6	20.9	41.8	35.0	60.5	44.2
Formate	14.6	7.5	40.1	22.5	64.2	52.5	85.4	60.0
Acetate	26.3	16.7	44.7	27.8	73.7	50.0	99.0	61.1
Propionate	37.1	22.9	48.6	31.7	77.1	59.3	99.3	80.0
Valerate	31.0	9.4	48.3	21.9	65.5	46.9	99.2	65.6
n-Butyrate	24.2	3.7	42.4	33.3	60.6	55.6	78.8	70.4
Malonate	32.4	22.9	73.0	54.3	99.2	77.2	100.0	100.0
Succinate	10.6	10.6	29.8	23.4	38.3	27.7	46.8	36.2
Oxalate	6.7	4.4	17.8	10.9	24.5	21.6	37.8	28.3
<b>p-Toluenediazonium salts:</b>								
Chloride	16.7	8.6	21.0	15.0	40.2	25.7	57.2	42.4
Formate	20.2	15.3	37.8	27.9	62.2	54.3	77.9	65.2
Acetate	11.7	7.0	23.3	16.4	39.4	34.8	60.4	55.7
Propionate	26.8	24.7	51.2	38.7	79.9	63.9	94.8	83.5
n-Butyrate	39.3	29.5	57.8	54.0	92.3	83.9	97.6	91.1
Valerate	36.9	28.3	57.1	54.2	85.9	77.2	94.5	94.5
Malonate	39.3	33.1	79.0	77.9	100.0	100.0	—	—
Succinate	14.7	7.4	24.3	17.2	33.9	29.1	53.6	51.1
Oxalate	16.3	13.5	23.2	20.2	36.5	31.2	52.0	42.1
<b>p-Nitrobenzenediazonium salts:</b>								
Chloride	18.6	6.2	29.0	20.6	41.6	26.9	57.9	37.3
Formate	21.6	10.8	34.6	19.4	49.7	30.3	64.8	43.2
Acetate	15.8	11.0	31.7	19.9	42.9	35.4	58.7	44.2
Propionate	31.4	21.5	49.6	34.9	75.6	50.9	88.6	61.6
n-Butyrate	30.6	12.9	48.4	30.6	63.6	50.9	81.3	68.6
Malonate	64.0	44.6	100.0	73.3	—	100.0	—	—
Succinate	19.0	10.2	30.8	17.9	54.4	30.6	66.1	48.4
Oxalate	13.5	4.4	24.9	13.2	40.7	22.1	49.7	33.9

The isolation of the double salts of the diazo compounds with mercuric chloride and the investigation of the stability of the diazo solutions to irradiation and storage in the dark was carried out as described earlier [1].

#### SUMMARY

1. The diazotization of amines with sodium nitrite in monobasic and dibasic saturated carboxylic acids has been studied. The greatest effect on diazotization is connected with a high dissociation constant of the acid. Weak acids (for example, propionic) greatly complicate the diazotization reaction by the formation of the diazoamino compounds.

2. A series of diazo compounds has been isolated in the solid state form of double salts of diazonium carboxylates with mercuric chloride.

3. The stability of aqueous solutions of diazonium carboxylates to the action of light and storage in the dark has been established.

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# INVESTIGATIONS IN THE FIELD OF DIAZO COMPOUNDS

## XV. THE DIAZOTIZATION OF AROMATIC AMINES WITH NITRITE IN HYDROXY-CARBOXYLIC ACIDS\*

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Having established the features of the diazotization of aromatic amines with nitrite in various saturated carboxylic acids [1], we carried out similar experiments in hydroxyacids. The possibility of using the latter for the diazotization of amines with nitrite without the participation of mineral acids has been illustrated in the literature by only single examples.

It was established that diazotization in aqueous solutions of hydroxyacids (0.04 g-mole in 100 ml) with a concentrated nitrite solution proceeds absolutely smoothly. Almost all amines form water-soluble salts with the various hydroxyacids. Only  $\alpha$ -naphthylamine forms sparingly soluble salts with citric and tartaric acids, and its diazotization was therefore carried out initially in suspension. The diazonium salts of hydroxyacids are all very soluble in water. The mean figures of three experiments on the diazotization of some amines in hydroxyacids are given in Tables 1 and 2.

The diazotization effect in various hydroxyacids is in agreement with the dissociation constants of the hydroxyacids and decreases in the order: lactic>citric>malic>tartaric>glycolic.

TABLE 1

Amine	Yield of diazo compound, %			
	time, min			
	5	15	30	60
Tartaric acid (0.04 g-mole)				
Sulfanilic acid	87.4	92.6	100.0	100.0
p-Aminobenzoic acid	63.7	69.4	83.7	100.0
$\alpha$ -Naphthylamine*	32.1	43.7	50.6	57.4
Citric acid (0.04 g-mole)				
Sulfanilic acid	89.6	94.3	100.0	100.0
p-Aminobenzoic acid	66.1	70.3	81.0	93.6
$\alpha$ -Naphthylamine*	33.1	38.6	45.6	51.3

\* Initial diazotization in suspension.

Some exception is observed in the diazotization of nitroanilines with tartaric acid, when the latter takes the place of citric acid in the above series according to its reaction velocity. All the hydroxyacids give a higher diazotization velocity than the saturated carboxylic acids corresponding to them in structure. This is in complete agreement with the greater dissociation constants of the hydroxyacids. In addition, the maximum yield of diazo compounds (for example, for p-toluidine or p-nitroaniline) with hydroxyacids is always lower than in diazotization in formic acid [1]. In spite of the fact that the electrolytic dissociation constants of citric and lactic acids are five

\*XIVth Communication: ZhOKh 31, 2212 (1961).

times higher, that of malic two times higher, and that of tartaric six times higher than that of formic acid, the specific properties of the latter ensure a high diazotization velocity.

The comparative diazotization in various hydroxyacids was carried out with 0.04 g-mole of hydroxyacid to 0.01 g-mole of amine, without taking the basicity of the acid into account. A diazotization experiment with 0.04 g-equiv. of citric acid gives quite a high result and does not disturb the rules given above relating to the diazotization velocity as a function of the dissociation constants of the hydroxyacids (Table 3).

TABLE 2

Hydroxyacid	Yield of diazo compound, %			
	time, min			
	5	15	30	60
<b>Aniline</b>				
Glycolic•	58.3	64.1	70.8	72.3
Lactic	67.3	75.9	85.7	99.1
Malic••	42.4	51.3	58.4	59.8
Tartaric•••	42.6	52.1	59.4	68.3
Citric••••	51.3	62.3	68.4	72.6
<b>p-Toluidine</b>				
Glycolic	48.2	53.8	78.7	82.1
Lactic	79.4	87.7	98.4	100.0
Malic	58.2	65.4	76.9	96.0
Tartaric	58.4	63.0	72.3	96.8
Citric	73.7	80.6	89.1	92.3
<b>p-Nitroaniline</b>				
Glycolic•••••	75.1	76.3	78.4	77.6
Lactic	95.1	97.4	98.4	100.0
Malic	83.5	87.2	96.6	100.0
Tartaric	84.0	97.2	98.1	100.0
Citric	81.1	98.2	94.9	99.7

•In addition to the diazo compound, the diazoamino compounds were obtained with respective yields (in %) of: 9.6, 13.3, 20.7, 27.7.

••The same: 8.1, 10.6, 8.9, 11.3.

•••The same: 2.2, 4.8, 7.7, 8.2.

••••The same: 1.3, 3.6, 4.8, 4.8.

•••••The same: 6.9, 10.3, 12.1, 11.9.

TABLE 3

Citric acid	Yield of diazo compound, %			
	p-toluidine diazotization time, min			
	5	15	30	60
0.04 g-mole	73.7	80.6	89.1	92.3
0.04 g-equiv.	62.1	68.4	84.3	86.6

TABLE 4

Double salt	% Hg		Diazo N, %		Characteristics of the substance	Ignition tempera- ture
	found	calc.	found	calc.		

Tartrates						
$C_6H_5-N_3-Ac \cdot HgCl_2 \bullet$	38.27	38.15	5.48	5.33	Plates	96-97°
$p-CH_3-C_6H_4-N_3-Ac \cdot HgCl_2$	37.41	37.16	5.31	5.19	Large plates	109-110
$p-O_2N-C_6H_4-N_3-Ac \cdot HgCl_2$	35.52	35.15	5.15	4.91	Fine yellow needles	118-119
$p-HOOC-C_6H_4-N_3-Ac \cdot HgCl_2$	35.47	35.22	5.27	4.92	Plates	106-107
$\alpha-C_6H_5-N_3-Ac \cdot HgCl_2$	35.23	34.84	4.82	4.84	Bright yellow plates	127-128

Citrates						
$C_6H_5-N_3-Ac \cdot HgCl_2 \bullet\bullet$	35.48	35.34	5.07	4.93	Small platelets	99-101
$p-CH_3-C_6H_4-N_3-Ac \cdot HgCl_2$	34.72	34.49	5.12	4.81	Large plates	114-115
$p-O_2N-C_6H_4-N_3-Ac \cdot HgCl_2$	33.08	32.75	4.86	4.57	Small yellow platelets	121-122
$p-HOOC-C_6H_4-N_3-Ac \cdot HgCl_2$	32.84	32.80	4.73	4.58	Large plates	110-111
$\alpha-C_6H_5-N_3-Ac \cdot HgCl_2$	32.61	32.48	4.86	4.53	Grey plates	131-132

$\bullet Ac = OOC(CHOH)_2COOH$ .

$\bullet\bullet Ac = OOCCH_2CH_2(OH)(COOH)_2$ .

The diazotization of aniline in all hydroxyacids is complicated by the formation of considerable amounts of the diazoamino compound, this tendency corresponding to the reverse of the sequence of hydroxyacids given above. For weakly basic amines, this tendency to form certain amounts of diazoamino compounds is observed only in glycolic acid. It is interesting to note that while  $\alpha$ -naphthylamine, on diazotization in such carboxylic acids as propionic or acetic, formed an azo dye in addition to the diazo compound, its diazotization in lactic, tartaric and citric leads to the formation of the diazo compound alone. However, diazotization of  $\alpha$ -naphthylamine in glycolic acid is accompanied by copious formation of a dye. The capacity of certain amines for maximum diazotization in various hydroxyacids increases with the presence in the nucleus of various substituents, in the sequence:  $SO_2OH > NO_2 > COOH > CH_3$ .

Aniline and  $\alpha$ -naphthylamine are the most difficult to diazotize in hydroxyacids. The series of diazonium salts of tartaric and citric acid was isolated in the solid state in the form of double salts with mercuric chloride (Table 4). The action of the light of a 500 w electric lamp on aqueous solutions of the diazo compounds at 20°, and also storage of similar solutions in closed containers in the dark at the same temperature, showed (Table 5) that the stability of the diazo compounds is largely connected, as was noted above for the rate of diazotization, with the dissociation constants of the hydroxyacids. The higher the dissociation constant of the hydroxyacid and, consequently, that of the acid anion of this acid in the diazo compounds, the higher the stability to light and storage which these diazonium salts possess. This may be observed very clearly on the basis of the stability of the series of diazo compounds from p-nitroaniline. A somewhat altered picture of the stability can be observed for aniline and p-toluidine. However, this is also connected with the different dissociation constants of the anions of these hydroxyacids in the diazo compounds of these basic amines. This behavior of diazonium salts of hydroxyacids is different from the stability of the diazonium salts of the corresponding saturated carboxylic acids, for which a dependence on the molecular weight of the carboxylic acid is characteristic. In addition, on comparing the stability of the diazonium salts of hydroxyacids and of the corresponding carboxylic acids, it is impossible not to notice the great difference in stability of the two types of diazo compound, apart from the diazonium lactates, the stability of which is several times higher than the stability of the diazonium propionates.

TABLE 5

Diazonium salt	Decomposition of diazo compound, % of initial							
	time of irradiation with 500 w lamp, hr							
	0.5		1.0		2.0		3.0	
	in light	in dark	in light	in dark	in light	in dark	in light	in dark
<b>Benzenediazonium salts:</b>								
Glycolate	7.4	4.3	14.9	10.6	21.3	17.0	38.0	23.4
Lactate	11.9	9.1	23.8	20.5	35.7	34.1	47.6	40.9
Malate	21.4	14.3	31.0	26.2	52.4	42.9	66.7	59.5
Tartrate	11.4	6.8	20.5	15.9	40.9	34.1	56.8	47.7
Citrate	12.8	7.9	23.1	13.2	35.9	31.6	46.2	44.7
<b>p-Toluenediazonium salts:</b>								
Glycolate	15.7	9.1	26.8	22.4	39.9	35.5	60.0	53.3
Lactate	23.2	17.5	33.7	26.2	46.4	39.1	63.6	54.3
Malate	29.0	20.2	39.9	35.5	60.0	48.8	75.6	55.5
Tartrate	12.4	8.7	21.0	15.3	38.0	24.1	63.7	54.3
Citrate	19.7	3.3	34.7	6.8	49.9	12.3	58.7	18.0
<b>p-Nitrobenzenediazonium salts:</b>								
Glycolate	17.3	12.7	32.5	23.3	47.5	38.1	64.7	46.5
Lactate	12.1	2.4	19.5	12.1	33.9	26.7	55.7	41.2
Malate	15.4	7.9	25.5	17.9	40.7	30.6	63.6	43.3
Tartrate	17.1	9.7	26.7	24.3	41.2	33.9	58.1	48.4
Citrate	14.1	4.8	26.7	17.1	41.2	29.1	60.5	43.6

## SUMMARY

1. The possibility of diazotizing aromatic amines with nitrite in various hydroxycarboxylic acids has been established.
2. Double salts of diazonium tartrates and citrates with mercuric chloride have been isolated.
3. The stability of solutions of the diazo compounds with anions of hydroxycarboxylic acids to light and to storage in the dark has been determined.

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## SYNTHESIS OF N-SUBSTITUTED METHACRYLAMIDES

### V. N,N'-ALKYLENEDIMETHACRYLAMIDES

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N-substituted methacrylamides were synthesized earlier from primary and secondary amines [1]. In the present paper the synthesis of a series of alkylenedimethacrylamides is reported. Of the compounds of this series, hexamethylenedimethacrylamide (HMDMA) has been previously obtained [2]. The synthesis of the diacryloyl and dimethacryloyl derivatives of aliphatic diamines, apart from that mentioned above, is not mentioned in the literature.

Diacyl derivatives of diamines from other acids are generally obtained by the reaction of the diamines with the anhydrides or the chlorides of these acids. The following have also been used as acylating agents: phenylacetic acid [3] and the chlorides of chloroacetic [4], cinnamic [5] and  $\beta$ -chloropropionic acids [6]. In addition, some diacyl derivatives of 1,2-diamines have been obtained by an indirect method [7].

We synthesized dimethacrylamides from ethylenediamine, 1,2-propylenediamine and decamethylenediamine. We used the chloride (MAC) and anhydride (MAA) of methacrylic acid as acylating agents. In the reaction of the diamines with MAC, alkylenediamine was used to bind the liberated hydrogen chloride: 1 g-mole of diamine was required for 1 g-mole of MAC.

The alkylenediamines are highly basic: ethylenediamine (EDA) has  $pK$  4.07 [8,9], trimethylenediamine 3.46 [8] and hexamethylenediamine 3.07 [9]. Although the  $pK$  of decamethylenediamine (DMDA) is not known, apparently its magnitude is of the same order as that of hexamethylenediamine [9,10]. In consequence of the high basicity of the alkylenediamines, their reaction with MAC is extremely exothermic and requires cooling. In the reaction of ethylenediamine and 1,2-propylenediamine with MAC in benzene with external cooling of the mixture by ice water, ethylenedimethacrylamide (EDMA) and 1,2-propylenedimethacrylamide (PDMA) are obtained. On acylating 1,2-propylenediamine with methacrylic anhydride in benzene, PDMA could not be isolated directly at the end of the reaction in consequence of its solubility in the methacrylic acid forming one of the reaction products. Only when the solution had stood for a long time did a precipitate of PDMA slowly separate. On the reaction of EDA and PDMA with 2 moles of methacrylic anhydride in anhydrous benzene, EDMA and DMDMA were obtained in high yields. It was also found that EDA reacts with methacrylic acid, giving a salt. This was shown by elementary analysis of the compound obtained and by the determination of the double bonds by the bromination method. However, in the literature it is indicated that EDA reacts with methyl methacrylate and acrylonitrile by addition to the double bond [11].

All the monomers obtained polymerized in the presence of initiators of the free-radical type forming polymers which were insoluble in organic solvents and decomposed without melting on heating above 300°.

#### EXPERIMENTAL

Propylenedimethacrylamide (PDMA). a) In a two-necked round-bottomed flask fitted with a mechanical stirrer, a reflux condenser and a dropping funnel were placed 7.4 g (0.1 g-mole) of propylenediamine in 40 ml of benzene. With stirring and external cooling of the mixture by ice water, 10.4 g (0.1 g-mole) of methacrylic chloride was added dropwise over 2 hours. (When the experiment is carried out without cooling, a polymer is formed.) Stirring was continued for a further 1-2 hours at room temperature. The precipitate of propylenediamine hydrochloride was filtered off and washed repeatedly with benzene, the benzene extracts were combined and the benzene was distilled off. The yield was 6.9 g (65.7%); m.p. 103-103.5° (from benzene) (to avoid the polymerization of the PDMA, its recrystallization was carried out in relatively large amounts of benzene in the presence of powdered copper). PDMA is soluble in water, ether, benzene, alcohol, acetone, dioxane, dimethylformamide and tetrahydrofuran in the cold, and in benzene and petroleum ether at the boil.

Found %: C 63.12, 63.19; H 8.75, 8.51; N 13.04, 13.00.  $C_{11}H_{18}O_2N_2$ . Calculated %: C 62.85; H 8.57; N 13.34.

b) In a flask was placed 0.74 g (0.01 g-mole) of propylenediamine in 20 ml of anhydrous benzene. With stirring and external cooling with ice water, 3.08 g (0.02 g-mole) of methacrylic anhydride (b.p. 65-67° at 3 mm) was added dropwise. On the addition of the first drops of the anhydride, the appearance of a precipitate was observed, but this then dissolved in the methacrylic acid liberated in the reaction.

On standing for 2 weeks, the solution slowly deposited a white precipitate of propylenedimethacrylamide with m.p. 102-103°. Yield 42%. All subsequent experiments were carried out in the same apparatus and under similar conditions.

Ethylenedimethacrylamide (EDMA). a) To 3 g (0.05 g-mole) of ethylenediamine in 30 ml of benzene, 5.2 g (0.05 g-mole) of methacryloyl chloride was added dropwise. The precipitate which separated consisted of a mixture of ethylenediamine hydrochloride and ethylenedimethacrylamide; the latter was separated by repeated boiling with benzene. Yield 2.15 g (47.5%); m.p. 172-173° (from benzene; polymerizes). It is soluble in alcohol, water, chloroform, acetone, ether, dimethylformamide and dioxane in the cold, and in benzene and nitromethane on heating; it is insoluble in benzene.

Found %: C 61.21, 61.38; H 7.87, 8.11; N 14.21, 14.38.  $C_{10}H_{16}O_2N_2$ . Calculated %: C 61.22; H 8.16; N 14.29.

b) Ethylenedimethacrylamide was obtained from 0.02 g-mole of ethylenediamine in 40 ml of benzene and 0.04 g-mole of methacrylic anhydride in a yield of 2.88 g (74.1%).

Salt of ethylenediamine and methacrylic acid. To 1.5 g (0.025 g-mole) of EDA in 20 ml of benzene was added 4.3 g (0.05 g-mole) of methacrylic acid (exothermic reaction). The precipitate which separated was filtered off, washed with benzene and dried. The yield was quantitative; m.p. 138.5-141°. The content of double bonds, determined by bromination, was 99.05%.

Found %: C 51.91, 51.66; H 8.65, 8.45; N 12.12, 12.02.  $C_{10}H_{20}O_4N_2$ . Calculated %: C 51.72; H 8.62; N 12.07.

Hexamethylenedimethacrylamide (HMDMA) [2]. a) A yield of 2.8 g (44.5%) was obtained from 0.05 g-mole of hexamethylenediamine in 30 ml of water and 0.05 g-mole of methacryloyl chloride; m.p. 115-115.5° (from benzene). It dissolves in the cold in acetone, alcohol, dimethylformamide, chloroform and tetrahydrofuran, and on heating in benzene and petroleum ether; it is insoluble in water.

Found %: C 67.20, 66.91; H 9.50, 9.81; N 11.03, 10.84.  $C_{14}H_{24}O_2N_2$ . Calculated %: C 66.6; H 9.55; N 11.1.

b) A yield of 6.75 g (53%) was obtained from 0.05 g-mole of hexamethylenediamine in 40 ml of dry benzene and 0.1 g-mole of methacrylic anhydride.

Decamethyldimethacrylamide (DMDMA). To 0.01 g-mole of decamethylenediamine freshly distilled in vacuo (m.p. 59-60°) in 30 ml of dry benzene, 0.02 g-mole of methacrylic anhydride was added dropwise. Yield 2.2 g (71.2%); m.p. 111.5-112° (from 50% alcohol).

It dissolves in alcohol, chloroform, dioxane and dimethylformamide in the cold, and in benzene and 50% aqueous alcohol on heating; it is insoluble in water.

Found %: C 70.42, 70.57; H 10.50, 10.36; N 9.18, 9.03.  $C_{18}H_{32}O_2N_2$ . Calculated %: C 70.13; H 10.39; N 9.09.

#### SUMMARY

The reaction of aliphatic diamines with the anhydride and chloride of methacrylic acid has been studied. Ethylene-, 1,2-propylene- and decamethylenedimethacrylamides, previously unreported in the literature, have been synthesized and characterized.

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## SYNTHESIS OF N-SUBSTITUTED METHACRYLAMIDES

### VI. N-METHYLDIMETHACRYLAMIDE

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The acetylation of acrylamide and methacrylamide with ketone [1] and of methacrylamide and  $\alpha$ -fluoroacrylamide with acetic anhydride [2] is reported in the literature. Full diacylamides of substituted acrylic acids are unknown.

The diacylamides of saturated monobasic acids are obtained by the reaction of nitriles with acids [3] and of amides and sodioamides with acid chlorides [4]. Acylation of amides with anhydrides is catalyzed by acids [5], but, using this process, nitriles are sometimes obtained [6]. The complexes of acyl chlorides with pyridine lead to the formation of di- and triacylamides [7]. The mechanism of the acylation of amides cannot be considered as established, although it has been studied recently [8].

Our attempts to carry out the acylation of methacrylamide and its N-alkyl or N-aryl-substituted derivatives by the action of methacryloyl chloride on them were not crowned with success. By acylating methacrylamide with methacrylic anhydride, we obtained a mixture of products which was difficult to separate and in which methacrylonitrile was found. On acylating methylmethacrylamide with methacrylic anhydride at 145-150°, methyldimethacrylamide was obtained. Methyldimethacrylamide may be obtained on heating methylamine hydrochloride with an excess of methacryloyl chloride (MAC). If methylamine hydrochloride is heated with equimolecular amounts of MAC in a solvent, the reaction leads smoothly to the formation of the monoacyl derivative—methylmethacrylamide. However, in both cases the reaction goes slowly and even on long heating about half the methylamine hydrochloride remains unchanged. Up to the present time this reaction has been reported only for the production of monoacyl derivatives of monobasic acids [9].

#### EXPERIMENTAL

N-Methyldimethacrylamide [ $\text{CH}_2=\text{C}(\text{CH}_3)\text{CO}_2\text{N}(\text{CH}_3)$  (MDMA)]. a) From methylmethacrylamide and methacrylic anhydride. In a two-necked flask fitted with a reflux condenser with a calcium chloride tube and a thermometer were placed methylmethacrylamide (0.15 g-mole) and methacrylic anhydride; to prevent polymerization, pyrogallol (0.01 g) and copper turnings were added. The contents of the flask were heated for 1.5 hours at 145° (in the reaction mass). At the end of the heating, the mixture formed a viscous dark green mass, from which ~30% of methyldimethacrylamide was isolated by freezing out. The filtrate after the removal of the crystals was subjected to vacuum distillation, fractions containing methacrylic acid and its anhydride being collected, and then fractions boiling up to 75° (1 mm). After they had stood in the refrigerator, a further small amount of MDMA crystallized out from the latter fraction in the form of fine colorless needles. The mass remaining in the distillation flask was polymer.

After two recrystallizations from heptane (or from aqueous alcohol), large colorless crystals with m.p. 90.5-91.5° (corrected) separated.

Found %: C 65.04, 64.80; H 7.88, 7.86; N 8.39, 8.38.  $\text{C}_9\text{H}_{13}\text{O}_2\text{N}$ . Calculated %: C 64.67; H 7.78; N 8.38.

The substance dissolves in the cold in acetone, ether, alcohol, benzene, dioxane and chloroform, and, on heating, in heptane and aqueous alcohol; it is insoluble in water. It is capable of polymerizing in the mass and in concentrated solutions, giving a soluble and fusible polymer not containing unsaturation.

b) From methylamine hydrochloride and methacryloyl chloride (according to G. M. Chetyrkina's directions). In a round-bottomed flask with a reflux condenser were placed 6.75 g (0.1 g-mole) of finely ground methylamine hydrochloride (MHC1), 22.9 g (0.22 g-mole) of methacryloyl chloride (MAC), and pyrogallol and copper turnings,

as polymerization inhibitors. The mixture was heated for 6 hours at an oil bath temperature of 110-120°. All the MHCl gradually went into solution. After cooling, the excess of MAC was distilled off from the reaction flask and the MDMA was extracted from the residual viscous mass by repeated heating with hexane; it crystallized out when the hexane solution was cooled in an amount of 5.8 g (34.8%). The MDMA melted at 89.0-90°.

On boiling 0.1 g-mole of MHCl and 0.11 g-mole of MAC with 35 ml of anhydrous toluene with stirring for 10 hours, part of the MHCl remained unchanged. After cooling, the MHCl residue was filtered off. When the solvent had been distilled off from the filtrate, the residual oil was fractionated in vacuo. The fraction boiling at 74-82° at 2 mm had  $n_D^{20}$  1.4740 (methylethacrylamide). At the same time, a small amount of MDMA (m.p. 88.5-90°) crystallized in the condenser.

On carrying out the reaction in benzene (16 hours' boiling), a product was obtained which distilled at 64-67° (1.5 mm) and had  $n_D^{20}$  1.4730 with a yield of ~45%.

Methacrylic anhydride. This was obtained by a somewhat modified method [10], starting from equimolecular amounts of methacrylic acid, its chloride and pyridine. The absence of an excess of pyridine made it possible to dispense with the washing of the ethereal solution of the anhydride with hydrochloric acid and water. After the completion of the reaction, the mass was allowed to stand in the cold for a day; the pyridine hydrochloride which separated out was filtered off and washed with dry ether. After the ether had been distilled off, the filtrate was fractionated: the fraction boiling at 83-84° (10 mm) was collected. Yield 66%.

#### SUMMARY

N-Methyldimethacrylamide, previously unreported in the literature, has been obtained by two methods and characterized.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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# SOME NEW TYPES OF ARBUZOV REARRANGEMENT

## XIII. THE REACTION OF TRIALKYL PHOSPHITES WITH o- AND p-NITROBENZALDEHYDES

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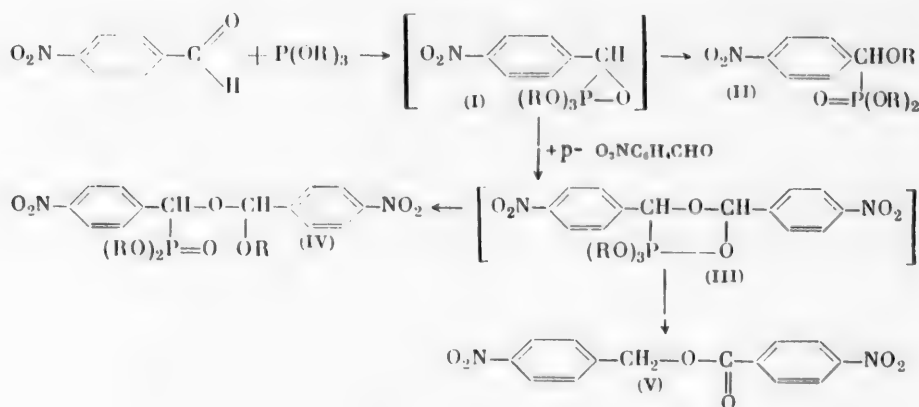
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The capacity of aldehydes for adding trialkyl phosphites was first shown by V. S. Abramov [1]. It has also been established that the carbonyl group readily adds trialkyl phosphites if it is conjugated with another carbonyl group [2]. It was of interest to study how an aldehyde group conjugated with a nitro group would behave in the reaction with phosphites. It is known that halogenonitro compounds [3] react with phosphites extremely energetically. It could be expected that systems possessing the conjugation  $O=N-(C=C)_n-C=O$  would also prove extremely reactive with respect to trialkyl phosphites.

A study of the reaction of o- and p-nitrobenzaldehydes with trialkyl phosphites showed that they react with one another extremely energetically even at room temperature. The reaction is complicated and leads to the production of very diverse products, depending on the experimental conditions and the structure of the initial reactants (particularly on the ester radical of the phosphite). The reactions of o- and p-nitrobenzaldehydes with trimethyl phosphite proceed in the simplest manner. In both cases, the product of the addition of trimethyl phosphite to the nitrobenzaldehyde is obtained (scheme 1, II; scheme 2, VI)—the methyl ester of the corresponding  $\alpha$ -methoxynitrobenzylphosphonic acid.

SCHEME 1



Triethyl phosphite reacts with nitrobenzaldehydes in a completely different fashion. On carrying out the reaction of triethyl phosphite with p-nitrobenzaldehyde at room temperature, some time after mixing the reagents a crystalline precipitate begins to separate which does not contain phosphorus and corresponds, in elementary analysis, to the initial aldehyde, but has a far higher melting point, gives the qualitative reaction for the nitro group and does not give the qualitative reactions for the alcohol, the aldehyde, or the ketone group. The infrared spectrum of this compound lacks an absorption band in the  $3200-3600\text{ cm}^{-1}$  region, which also confirms the absence of a hydroxyl group in it. The carbonyl group exhibits absorption at  $1706\text{ cm}^{-1}$ , which, in conjunction with the absence of the



$$\begin{array}{c}
 \text{NO}_2 \\
 | \\
 \text{C}=\text{O} \\
 | \\
 \text{H} \\
 \text{---} \text{P(OR)}_3 \longrightarrow \left[ \begin{array}{c} \text{NO}_2 \\ | \\ \text{CH} \\ | \\ \text{O} \end{array} \right] \text{P(OR)}_3 \text{---} \text{O} \longrightarrow \begin{array}{c} \text{NO}_2 \\ | \\ \text{CH} \text{---} \text{OR} \\ | \\ \text{O}=\text{P(OR)}_2 \end{array} \text{ (VI)} \\
 \downarrow + \sigma\text{-O}_2\text{NC}_6\text{H}_4\text{CHO} \\
 \begin{array}{c} \text{NO}_2 \\ | \\ \text{CH} \text{---} \text{O} \text{---} \text{CH} \text{---} \text{O} \text{---} \text{P(OR)}_3 \end{array} \text{ (VII)} \xrightarrow[\text{Heat}]{\text{ROH}} \begin{array}{c} \text{NO}_2 \\ | \\ \text{CH} \text{---} \text{CH} \text{---} \text{O} \text{---} \text{P(OR)}_3 \end{array} \text{ (VIII)} + \text{OP(OR)}_3 \\
 \downarrow \\
 \begin{array}{c} \text{NO}_2 \\ | \\ \text{CH} \text{---} \text{O} \text{---} \text{CH} \text{---} \text{O} \text{---} \text{P(OR)}_2 \end{array} \text{ (IX)} \xrightarrow{+\text{H}_2\text{O}} \begin{array}{c} \text{NO}_2 \\ | \\ \text{CH} \text{---} \text{O} \text{---} \text{CH} \text{---} \text{OH} \\ | \\ \text{P(OR)}_2=\text{O} \end{array} \text{ (X)}
 \end{array}$$

qualitative reaction for ketonic oxygen compels the presence of an acid or ester carbonyl group to be assumed. By the action of hydrogen bromide on this compound, p-nitrobenzyl bromide was obtained. All this permits the compound to be assigned the structure of the p-nitrobenzyl ester of p-nitrobenzoic acid (V). Consequently, trialkyl phosphites may bring about a reaction similar to Tishchenko's reaction in the series of aromatic aldehydes. A similar type of condensation takes place by the action of ammonium ethoxide in anhydrous benzene on o- and p-nitrobenzaldehydes [4].

On standing, the reaction mixture of p-nitrobenzaldehyde and triethyl phosphite begins to deposit crystals containing phosphorus and corresponding by analysis to the addition product of 2 molecules of p-nitrobenzaldehyde to 1 molecule of phosphite. The compound obtained does not give the qualitative reactions for the carbonyl and hydroxyl groups. Its structure, probably, may be expressed by formula (IV). Analogous products are obtained in the reactions with o-nitrobenzaldehyde (see Scheme 2, IX).

Tripropyl phosphite and tributyl phosphite react with p-nitrobenzaldehyde under similar conditions with the formation, mainly, of (V). It is possible that under these conditions products (IV) are also formed in part; however, these could not be isolated in pure form. The total process of the interaction of a trialkyl phosphite with p-nitrobenzaldehyde may be represented by scheme 1. The formation of the intermediate products (I) and (III) could not be confirmed; however, in the reaction with o-nitrobenzaldehyde, the product (VII) analogous to (III) was isolated. It was also impossible to establish the nature of the expelled phosphorus-containing part of the molecule in the conversion of (III) into (V). In all cases, the liquid part of the reaction products decomposed when attempts were made to distill it. It was established by a special experiment that catalytic amounts of triethyl phosphite cannot convert p-nitrobenzaldehyde into (V). The formation of (V) proceeds, in the main, only with a ratio of the initial reactants of 1:1; in the reaction of 2 moles of p-nitrobenzaldehyde with 1 mole of phosphite, the yield of (V) is considerably reduced as a result of an increased yield of (IV). It was possible to assume that oxygen would favor the elimination of phosphorus and the formation of (V). However, the presence of oxygen in the course of the reaction had practically no effect. Thus, the mechanism of the conversion of p-nitrobenzaldehyde into (V) is not completely explained; the scheme suggested is hypothetical. Since an excess of phosphite favors the formation of (V), it may be considered that the trialkyl phosphite plays a definite role in eliminating the phosphite from (III).

The reaction of triethyl phosphite with o-nitrobenzaldehyde proceeds in a different manner from that with p-nitrobenzaldehyde. On carrying out the reaction under mild conditions (in ethereal solution, without heating), a substance is formed which corresponds in analysis to the product of addition of 2 molecules of the nitrobenzaldehyde to 1 molecule of the phosphite. This compound is extremely unstable, and rapidly deliquesces to form a sticky mass. On being heated in ethereal solution, it is converted into an isomeric product possessing stable properties. An identical product is obtained on carrying out the reaction under more severe conditions. By analogy with the reactions of trialkyl phosphites with  $\alpha$ -diketones studied earlier, it may be assumed that the unstable product obtained under mild conditions is the intermediate addition product of 2 moles of the aldehyde to 1 mole of the phosphite (VII), and the second product has the structure (IX) and is the final product analogous to (IV). Compound (IX) is extremely resistant to the action of dilute acids and alkalis; it is decomposed by the action of concentrated alkali with the liberation of o-nitrobenzaldehyde; on saponifying it, no individual products at all could be isolated; it does not give the qualitative reactions for hydroxyl and does not react with sodium; determination of hydroxyl according to Verley (acetylation) gave a negative result. All these results, in conjunction with the results on the properties of the isomeric (IV), compel formula (IX) to be assumed for the product obtained.

The intermediate compound (VII), in a similar way to the intermediate products of the addition of trialkyl phosphites to  $\alpha$ -diketones described earlier, readily reacts with water with the formation of a substance corresponding in analysis to the product (X): in contrast to (IX), it gives the qualitative reaction for the hydroxyl group. On heating an alcoholic solution of (VII), a compound is formed which does not contain phosphorus and corresponds, according to the results of elementary analysis, to formula (VIII).

The presence of an  $\alpha$ -oxide ring is confirmed by the fact that the action of dry hydrogen chloride on (VIII) leads to the addition of the hydrogen chloride and the formation of a hygroscopic product crystallizing poorly.

By the action of tripropyl phosphite on o-nitrobenzaldehyde an unstable compound deliquescing in air (VII,  $R = n-C_3H_7$ ) was again obtained; by the action of alcohol on it, compound (VIII) obtained earlier showed no depression of the melting point. Likewise, the action of water yielded (X;  $R = n-C_3H_7$ ). However, (IX,  $R = n-C_3H_7$ ) could not be obtained. On carrying out the reaction under more severe conditions, (VII,  $R = n-C_3H_7$ ) was obtained and some (VIII) was formed.

Tributyl phosphite, on the other hand, only forms the stable product (IX), which undergoes no change on the action of moisture, alcohol, or heat.

Triphenyl phosphite reacts with p-nitrobenzaldehyde in a similar manner to trimethyl phosphite, forming the compound (II) only on prolonged heating; an intermediate product of type (I) could not be isolated.

Compound	Name	M. p.	% P	
			found	calculated
(II) $R = C_6H_5$ $C_{10}H_{14}O_6NP$	Dimethyl ester of 1-methoxy-1-(p-nitrophenyl)-methylphosphonic acid	132–134°	11.3	11.3
(VI) $R = C_6H_5$ $C_{10}H_{14}O_6NP$	Dimethyl ester of 1-methoxy-1-(o-nitrophenyl)-methylphosphonic acid	113–115	11.3	11.5
(II) $R = C_6H_5$ $C_{25}H_{20}O_6NP$	Diphenyl ester of 1-phenoxy-1-(p-nitrophenyl)-methylphosphonic acid	116–118	6.7	7.2
(IV) $R = C_2H_5$ $C_{20}H_{25}O_9N_2P$	Ethyl $\alpha$ -diethoxyphosphinyl-p-nitrobenzyl acetal of p-nitrobenzaldehyde	139–140	6.6	6.4
(IX) $R = C_2H_5$ $C_{20}H_{25}O_9N_2P$	Ethyl $\alpha$ -diethoxyphosphinyl-o-nitrobenzyl acetal of o-nitrobenzaldehyde	144–145	6.6	6.6
(X) $R = C_2H_5$ $C_{18}H_{21}O_9N_2P$	$\alpha$ -Diethylphosphinyl-o-nitrobenzyl semiacetal of o-nitrobenzaldehyde	140–142	7.1	7.1
(VII) $R = C_2H_5$ $C_{20}H_{25}O_9N_2P$	2,4-Di-o-nitrophenyl-5,5,5-triethoxy-5-phospha-1,3-dioxolan	120 (with decomp.)	6.6	6.5
(X) $R = n-C_3H_7$ $C_{20}H_{25}O_9N_2P$	$\alpha$ -Di-p-propoxyphosphinyl-o-nitrobenzyl semiacetal of o-nitrobenzaldehyde	128–130	6.6	6.4
(V) $C_{14}H_{10}O_6N_2$	p-Nitrobenzyl ester of p-nitrobenzoic acid	169–170	$\left\{ \begin{array}{l} \% C: 55.6 \\ \% H: 3.04 \end{array} \right.$	$\left\{ \begin{array}{l} 55.3 \\ 3.4 \end{array} \right.$
(IX) $R = n-C_4H_9$ $C_{26}H_{37}O_9N_2P$	n-Butyl $\alpha$ -dibutoxyphosphinyl-o-nitrobenzyl acetal of o-nitrobenzaldehyde	108	5.4	5.8
(VIII) $C_{14}H_{10}O_5N_2$	o,o'-Dinitrostilbene oxide	164–165	$\left\{ \begin{array}{l} \% C: 58.8 \\ \% H: 4.5 \end{array} \right.$	$\left\{ \begin{array}{l} 58.1 \\ 4.5 \end{array} \right.$
(VII) $R = n-C_3H_7$ $C_{23}H_{31}O_9N_2P$	2,4-Di-o-nitrophenyl-5,5,5-tri-propoxy-5-phospha-1,3-dioxolan	104–106	6.1	5.9

The constants of the compounds obtained and the analytical results are given in the table. The yields of the products are not shown in the table, since in the separation of the complex mixtures a considerable part of the reaction products is lost in the recrystallizations and washings, and the amounts of pure compounds obtained do not permit an idea to be gained as to which of the courses of the reaction is the main one and which a subsidiary one.

#### EXPERIMENTAL

Addition of trimethyl phosphite to p-nitrobenzaldehyde. To an ethereal solution of 5 g of p-nitrobenzaldehyde was added 4.1 g of trimethylphosphite and the reaction mixture was heated to the boil for 4 hours. After removal of the solvent, a crystalline precipitate separated out. Two recrystallizations from o-xylene yielded 2.6 g of a crystalline product with m.p. 132–134°. It does not give the qualitative reactions for the hydroxyl group and does not react with phenylhydrazine or 2,4-dinitrophenylhydrazine.

Found %: P 11.3.  $C_{10}H_{14}O_6NP$ . Calculated %: P 11.3.

Addition of trimethyl phosphite to o-nitrobenzaldehyde. To an ethereal solution of 3 g of o-nitrobenzaldehyde was added 2.5 g of trimethyl phosphite. After 30-50 minutes a crystalline precipitate began to separate and the temperature rose to 30-35°. The reaction was complete after 3 hours. The yield was 3.8 g. After recrystallization from o-xylene the product had m.p. 113-115°.

Found %: P 11.5.  $C_{10}H_{14}O_6NP$ . Calculated %: P 11.3.

Reaction of triethyl phosphite with p-nitrobenzaldehyde. To an ethereal solution of 7 g of p-nitrobenzaldehyde was added 7.5 g of triethyl phosphite. The reaction mixture was heated to the boil for 6 hours. Next day, a crystalline precipitate had separated. After recrystallization from o-xylene, 1.8 g of a substance with m.p. 169-170° was obtained. Literature data for the p-nitrobenzyl ester of p-nitrobenzoic acid: m.p. 171-172° [4].

Found %: C 55.3; H 3.4.  $C_{14}H_{10}O_6N_2$ . Calculated %: C 55.6; H 3.04.

The action of dry hydrogen bromide on 0.4 g of the fused crystals (m.p. 169-170°) led, after purification and recrystallization, to 0.1 g of p-nitrobenzyl bromide with m.p. 96-98°.

The ether was removed from the reaction mixture and after some days crystals began to separate which had m.p. 139-140° after purification.

Found %: P 6.4.  $C_{20}H_{25}O_9N_2P$ . Calculated %: P 6.6.

The product obtained underwent no change on boiling in alcohol or by the action of water. It also remained unchanged when heated with 10% HCl for 4 hours. It turned yellow when treated with a concentrated solution of NaOH and decomposed with the formation of p-nitrobenzaldehyde.

Performing the reaction between p-nitrobenzaldehyde and triethyl phosphite in the absence of a solvent led to the same results; on standing, the non-phosphorus-containing compound (V) first began to separate, then the content of phosphorus in the precipitate separating out slowly rose [as a mixture of (V) and (IV) separated] and finally, almost pure (IV) separated. Performing the reaction in vacuo led to the same results. When attempts were made to distill the liquid part of the reaction products, no individual substances could be isolated.

The experiments with tri-n-propyl and tri-n-butyl phosphites were carried out similarly. In both cases, only product (V) was obtained.

Reaction of triethyl phosphite with o-nitrobenzaldehyde. Experiment 1. To an ethereal solution of 7 g of o-nitrobenzaldehyde was added 7.5 g of triethyl phosphite, a rise of temperature to 35-40° being observed. The reaction mixture was left for 24 hours at room temperature. A crystalline precipitate separated. After it had been washed with petroleum ether, 4.2 g of sticky lamellar crystals deliquescent on standing in air (VII) were obtained; m.p. about 120° (with decomp).

Found %: P 6.5.  $C_{20}H_{25}O_9N_2P$ . Calculated %: P 6.6.

The liquid part of the reaction products was heated for several hours at the boiling point of ether. After cooling, a crystalline precipitate separated which was washed with petroleum ether and recrystallized; m.p. 144-145°.

Found %: P 6.6.  $C_{20}H_{25}O_9N_2P$ . Calculated %: P 6.6.

The substance remained unaltered when treated with water, alcohol, or dilute solutions of acids and alkalis. It is soluble in alcohol, acetone and benzene, and insoluble in xylene and petroleum ether. It does not contain hydroxyl groups (the qualitative reaction with aniline, acetylation with acetic anhydride and benzylation with benzoyl chloride gave negative results), and it does not react with 2,4-dinitrophenylhydrazine.

Experiment 2. The same amounts of initial reactants as in experiment 1 were heated in ethereal solution for some hours. After cooling, 2.7 g of a crystalline product with m.p. 142-145° was obtained.

Experiment 3. To an alcoholic solution of 1 g of o-nitrobenzaldehyde was added 1.2 g of triethyl phosphite. The reaction mixture was heated to the boil for 6 hours. After removal of the alcohol, crystals having m.p. 164-165° after purification were obtained.

Found %: C 58.1; H 4.5.  $C_{14}H_{10}O_5N_2$ . Calculated %: C 58.8; H 4.5.

The substance is insoluble in ether, alcohol, petroleum ether, xylene and water. It is vigorously decomposed by the action of acids. When a suspension of it is treated with dry hydrogen chloride, it adds on hydrogen chloride, a hy-

grosopic substance deliquescent in air being formed. A mixed melting point of the crystals with m.p. 164-165° with the crystals obtained by the action of alcohol on (VII, R=C<sub>2</sub>H<sub>5</sub> and n-C<sub>3</sub>H<sub>7</sub>) showed no depression of the melting point. It does not give the qualitative reactions for the hydroxyl or the carbonyl group.

Action of alcohol on (VII, R=C<sub>2</sub>H<sub>5</sub>). A solution of 0.3 g of the product (VII) in anhydrous ethanol was heated for several hours. After cooling, 0.2 g of crystals were separated which after purification had m.p. 163-165°. They were identical in properties with the crystals described in the previous experiment.

Reaction of tripropyl phosphite with o-nitrobenzaldehyde. Experiment 1. To an ethereal solution of 4 g of o-nitrobenzaldehyde was added 5.5 g of tripropyl phosphite. Some time after the addition of the phosphite, the temperature of the reaction mixture rose by 10°. The mixture was allowed to stand for 24 hours. After removing the ether, 4.2 g of substance were obtained. After petroleum ether washing, colorless crystals deliquescent in the air were obtained; m.p. 104-106°.

Found %: P 5.9. C<sub>23</sub>H<sub>31</sub>O<sub>9</sub>N<sub>2</sub>P. Calculated %: P 6.1.

On boiling the crystals obtained in solution in anhydrous propyl alcohol, a product with m.p. 163-165°, identical with that described in the previous experiment, was formed.

Action of water on (VII, R=n-C<sub>3</sub>H<sub>7</sub>). To a solution of 0.5 g of the crystalline product obtained in the previous experiment was added 0.5 ml of water. The temperature rose by 10°. After the solution had stood for some time, crystals separated out which had m.p. 128-130°. They gave the qualitative reaction with vanillin for the presence of a hydroxyl group. Yield 0.1 g.

Found %: P 6.4. C<sub>20</sub>H<sub>25</sub>O<sub>9</sub>N<sub>2</sub>P. Calculated %: P 6.6.

The reaction of (VII, R=C<sub>2</sub>H<sub>5</sub>) with water proceeded similarly.

Experiment 2. To 1 g of o-nitrobenzaldehyde was added 1.4 g of tripropyl phosphite. An increase in temperature of 20° was observed. The reaction mass was heated for 20 hours at 80-90°. After 24 hours, 0.4 g of crystals with m.p. 166-168° (from o-xylene) separated. They did not contain phosphorus. A mixed melting point test with the crystals with m.p. 163-165° obtained in experiment 1 gave no depression of the melting point. No stable non-deliquescent crystals containing phosphorus could be obtained from this reaction.

Reaction of tributyl phosphite with o-nitrobenzaldehyde. When 2.5 g of o-nitrobenzaldehyde was added to 5 g of tributyl phosphite, a spontaneous rise in the temperature to 80-90° took place. On standing, the reaction mass yielded a crystalline product. After purification, 0.7 g of a substance with m.p. 108° was obtained.

Found %: P 5.8. C<sub>26</sub>H<sub>37</sub>O<sub>9</sub>N<sub>2</sub>P. Calculated %: P 5.4.

The crystals did not deliquesce in air and did not change on boiling with alcohol, and were obviously (IX, R=n-C<sub>4</sub>H<sub>9</sub>).

Experiments to obtain (VII, R=n-C<sub>4</sub>H<sub>9</sub>) under milder conditions led to the production of crystals identical in properties and melting point with the product described above.

Addition of triphenyl phosphite to p-nitrobenzaldehyde. To 2 g of triphenyl phosphite in dry benzene was added 1 g of p-nitrobenzaldehyde. The reaction mixture was heated at 80-90° for 10 hours. The solvent was removed and, after standing for 4 hours, the whole mass crystallized.

Found %: P 7.2. C<sub>25</sub>H<sub>20</sub>O<sub>6</sub>NP. Calculated %: P 6.7.

#### SUMMARY

The reactions of trialkyl phosphites with o- and p-nitrobenzaldehydes have been studied. It has been established that, in the first stage, these reactions proceed in accordance with the Arbuzov rearrangement; further reactions proceed differently according to the structure of the initial reactants.

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# CATALYTIC SYNTHESIS OF HALOGEN DERIVATIVES OF β-ARYLAMINOKETONES

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The synthesis of β-arylamino ketones by the catalytic condensation of Schiff's bases with aliphatic-aromatic ketones has been described earlier [1].

The present work was devoted to the production of chloro, bromo and iodo derivatives of β-arylamino ketones (table), which should possess physiological activity [2]. For this purpose, the Schiff's bases obtained from o- and p-chloro-, p-bromo- and p-iodoanilines and various aromatic aldehydes were brought into reaction with acetophenone and its derivatives. The reaction was catalyzed by the hydrochlorides of the primary amines entering into the composition of the Schiff's bases.

It was established that the presence of a halogen in the para position to the nitrogen atom very strongly decreases the velocity of the hydramine cleavage into primary amine and the corresponding chalcone [3]. This is apparently due to the fact that a halogen atom, being conjugated with the π-electron of the benzene ring, transmits its influence to the nitrogen atom in the para position and thereby stabilizes the -NH-CH- bond, which has a high tendency to polarize.

## EXPERIMENTAL

Equimolecular amounts of the Schiff's base and the aliphatic-aromatic ketone (0.01 g-mole) in alcoholic solution were heated on the water bath for 30-40 minutes. The hydrochlorides of o- or p-aniline, p-bromoaniline or p-iodoaniline (0.5-1.0 g) were used as catalysts. After cooling in the refrigerator, the crystalline mass was washed with aqueous ammonia to destroy the catalyst. The water-washed product was recrystallized from a mixture of alcohol and benzene (1: 1). All the amino ketones synthesized formed white crystalline substances insoluble in water, very soluble in benzene, sparingly soluble in alcohol.

β-Arylamino ketone name	Empirical formula	M. p.	Yield, %	N content, % (Kjeldahl)	
				found	calculated
β-o-Chloroanilino-β-phenylpropio-phenone	C <sub>21</sub> H <sub>18</sub> ONCl	117°	15.5	4.28, 4.26	4.17
β-p-Chloroanilino-β-phenylpropio-phenone	C <sub>21</sub> H <sub>18</sub> ONCl	170	37.5	4.26, 4.54	4.17
p-Methoxyphenyl β-p-chloroanilino-β-phenylethyl ketone	C <sub>22</sub> H <sub>20</sub> O <sub>2</sub> NCl	175-176	29.3	3.78, 3.86	3.83
p-Ethoxyphenyl β-p-chloroanilino-β-phenylethyl ketone	C <sub>23</sub> H <sub>22</sub> O <sub>2</sub> NCl	129-130	21.0	4.01, 3.95	3.69
p-Chlorophenyl β-p-chloroanilino-β-phenylethyl ketone	C <sub>21</sub> H <sub>17</sub> ONCl <sub>2</sub>	131-132	38.2	3.95, 3.88	3.78
p-Bromophenyl β-p-chloroanilino-β-phenylethyl ketone	C <sub>21</sub> H <sub>17</sub> ONClBr	144-145	39.1	3.70, 3.77	3.38

(continued on next page)



(continued)

β-Arylaminoketones name	Empirical formula	M. p.	Yield, %	N content, % (Kjeldahl)	
				found	calcu- lated
p-Tolyl β-p-chloroanilino-β-phenylethyl ketone	C <sub>22</sub> H <sub>20</sub> ONCl	152—153	23.5	3.97, 4.07	4.01
β-p-Chloroanilino-β-phenylpropio-α-naphthone	C <sub>25</sub> H <sub>20</sub> ONCl	168—169	19.4	3.62, 3.62	3.63
β-p-Chloroanilino-β-p-methoxyphenylpropio-phenone	C <sub>22</sub> H <sub>20</sub> O <sub>2</sub> NCl	158	34.2	3.91, 3.87	3.83
p-Methoxyphenyl β-p-chloroanilino-β-p-methoxyphenyl ethyl ketone	C <sub>23</sub> H <sub>22</sub> O <sub>3</sub> NCl	132—133	31.6	3.50, 3.52	3.54
p-Bromophenyl β-p-chloroanilino-β-p-methoxyphenylethyl ketone	C <sub>22</sub> H <sub>18</sub> O <sub>2</sub> NClBr	109—110	38.8	3.17, 3.18	3.15
β-p-Bromoanilino β-phenylpropio-phenone	C <sub>21</sub> H <sub>18</sub> ONBr	182—183	37.5	3.66, 3.67	3.68
p-Methoxyphenyl β-p-bromoanilino-β-phenylethyl ketone	C <sub>22</sub> H <sub>20</sub> O <sub>2</sub> NBr	175—176	40.2	3.28, 3.33	3.42
β-p-Bromoanilino β-p-methoxyphenylpropio-phenone	C <sub>22</sub> H <sub>20</sub> O <sub>2</sub> NBr	170—171	33.8	3.20, 3.17	3.42
p-Bromophenyl β-p-anilino-β-phenylethyl ketone	C <sub>21</sub> H <sub>17</sub> ONBr <sub>2</sub>	152—153	45.0	3.11, 3.11	3.04
Phenyl β-p-iodoanilino-β-phenylethyl ketone	C <sub>21</sub> H <sub>18</sub> ONI	165—166	38.8	3.21, 3.26	3.28
p-Methoxyphenyl β-p-iodoanilino-β-phenylethyl ketone	C <sub>22</sub> H <sub>22</sub> O <sub>2</sub> NI	163—164	40.2	3.12, 3.12	3.07
p-Ethoxyphenyl β-p-iodoanilino-β-phenylethyl ketone	C <sub>23</sub> H <sub>22</sub> O <sub>2</sub> NI	161	45.0	2.89, 2.93	2.97
p-Chlorophenyl β-p-iodoanilino-β-phenylethyl ketone	C <sub>21</sub> H <sub>17</sub> ONClI	145—146	28.3	2.97, 3.02	3.03
p-Bromophenyl β-p-iodoanilino-β-phenylethyl ketone	C <sub>21</sub> H <sub>17</sub> ONBrI	162—163°	38.4	2.80, 2.84	2.77
p-Tolyl β-p-iodoanilino-β-phenylethyl ketone	C <sub>22</sub> H <sub>20</sub> NI	158	33.6	3.19, 3.23	3.17
Phenyl β-p-iodoanilino-β-(α-naphthyl)-ethyl ketone	C <sub>25</sub> H <sub>20</sub> ONI	167—168	32.2	3.11, 3.17	2.94
p-Methoxyphenyl β-p-iodoanilino-β-(α-naphthyl)-ethyl ketone	C <sub>26</sub> H <sub>22</sub> O <sub>2</sub> NI	132—133	21.9	2.71, 2.75	2.76
p-Chlorophenyl β-p-iodoanilino-β-(α-naphthyl)-ethyl ketone	C <sub>25</sub> H <sub>19</sub> ONClI	148—149	23.1	2.53, 2.54	2.73
p-Bromophenyl β-p-iodoanilino-β-(α-naphthyl)-ethyl ketone	C <sub>25</sub> H <sub>19</sub> ONBrI	123—124	19.8	2.48, 2.52	2.52

Hydramine cleavage was carried out in the following way: a mixture of 0.3-0.5 g of the aminoketone with 4-5 ml of concentrated hydrochloric acid was heated on the water bath until the crystalline material was completely converted into oil or, in individual cases, until the nature of the crystals had changed. At the end of the reaction, after cooling, the chalcone was filtered off, washed with water, and crystallized from alcohol. At the same time, the chalcones theoretically expected from the hydramine cleavage were synthesized [4] from the corresponding aromatic aldehydes and aliphatic-aromatic ketones. Tests of the melting points of mixtures of the chalcones synthesized with the substances obtained by hydramine cleavage gave no depression of the melting point.

#### SUMMARY

Twenty-five new chloro, bromo, and iodo derivatives of  $\beta$ -arylamino ketones have been obtained by the catalytic condensation of Schiff's bases with aliphatic-aromatic ketones.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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# THE CATALYTIC SYNTHESIS OF $\beta$ -ARYLAMINOKETONES

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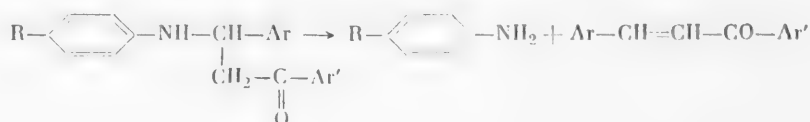
The catalytic synthesis of  $\beta$ -arylamino ketones by the condensation of Schiff's bases with aliphatic-aromatic ketones has been described in previous communications [1]. In the present work, methyl p-biphenyl ketone, selection of which is explained by the fact that biphenyl derivatives possess considerable physiological activity [2], was used for condensation with the Schiff's bases.

The following Schiff's bases were synthesized: benzylideneaniline, benzylidene-p-toluidine, benzylidene-m-toluidine, benzylidene-p-anisidine, benzylidene-m-nitroaniline, benzylidene-p-bromoaniline, benzylidene-p-iodoaniline, p-methylbenzylidene, p-methylbenzylidene-p-toluidine, p-methylbenzylidene-m-toluidine, p-methylbenzylidene-p-anisidine, p-methoxybenzylideneaniline, p-methoxybenzylidene-p-toluidine, p-methoxybenzylidene-m-toluidine.

The following  $\beta$ -arylamino ketones were obtained for the first time by the condensation of the Schiff's bases listed with methyl p-biphenyl ketone: p-biphenyl  $\beta$ -anilino- $\beta$ -phenylethyl ketone (I), p-biphenyl  $\beta$ -p-toluidino- $\beta$ -phenylethyl ketone (II), p-biphenyl  $\beta$ -m-toluidino- $\beta$ -phenylethyl ketone (III), p-biphenyl  $\beta$ -p-anisidino- $\beta$ -phenylethyl ketone (IV), p-biphenyl  $\beta$ -m-nitroanilino- $\beta$ -phenylethyl ketone (V), p-biphenyl  $\beta$ -p-bromoanilino- $\beta$ -phenylethyl ketone (VI), p-biphenyl  $\beta$ -p-iodoanilino- $\beta$ -phenylethyl ketone (VII), p-biphenyl  $\beta$ -anilino- $\beta$ -p-tolyethyl ketone (VIII), p-biphenyl  $\beta$ -p-toluidino- $\beta$ -p-tolyethyl ketone (IX), p-biphenyl  $\beta$ -p-toluidino- $\beta$ -p-tolyethyl ketone (X), p-biphenyl  $\beta$ -p-anisidino- $\beta$ -p-tolyethyl ketone (XI), p-biphenyl  $\beta$ -anilino- $\beta$ -p-methoxyphenylethyl ketone (XII), p-biphenyl  $\beta$ -p-toluidino- $\beta$ -p-methoxyphenylethyl ketone (XIII), p-biphenyl  $\beta$ -m-toluidino- $\beta$ -p-methoxyphenylethyl ketone (XIV).

The hydrochlorides of the amines entering into the composition of the Schiff's bases were used as catalysts.

All the  $\beta$ -arylamino ketones were subjected to hydramine cleavage: on heating with concentrated hydrochloric acid they split into the amine and the corresponding chalcone.



## EXPERIMENTAL

Methyl p-biphenyl ketone was synthesized according to data in the literature [3].

**$\beta$ -Arylamino ketones.** A solution of 0.01 g-mole of methyl p-biphenyl ketone in 7-10 ml of alcohol was poured into a solution of 0.01 g-mole of the Schiff's base in 10-15 ml of alcohol heated on the water bath, and 0.5-1.0 g of the hydrochloride of the amine was added. The reaction mixture was heated on the water bath for 0.5-1 hour. The precipitate which separated when the mixture was cooled in the refrigerator was filtered off, treated with ammonia solution, and crystallized from a mixture of alcohol and benzene or toluene. The results obtained and the constants of the compounds synthesized are given in the table.

**Hydramine cleavage** of the  $\beta$ -arylamino ketones synthesized was carried out by the method described earlier.

The cleavage of (I-VII) led to 4-phenylchalcone with m.p. 154-155°. The cleavage of (VIII-XI) led to 4-phenyl-4'-methylchalcone with m.p. 179-180°. The cleavage of (XII-XIV) led to 4-phenyl-4'-methoxychalcone with m.p. 142-144°.

No.	$\beta$ -Arylamino ketones (R=C <sub>6</sub> H <sub>4</sub> -C <sub>6</sub> H <sub>4</sub> -p)	M. p.	Yield, %	N content, %	
				found	calculated
I	$\begin{array}{c} \text{C}_6\text{H}_5-\text{NH}-\text{CH}-\text{C}_6\text{H}_5 \\   \\ \text{CH}_2-\text{CO}-\text{R} \end{array}$	174-175°	35	3.53, 3.53	3.71
II	$\begin{array}{c} \text{p-CH}_3-\text{C}_6\text{H}_4-\text{NH}-\text{CH}-\text{C}_6\text{H}_5 \\   \\ \text{CH}_2-\text{CO}-\text{R} \end{array}$	186-187	40	3.37, 3.47	3.57
III	$\begin{array}{c} \text{m-CH}_3-\text{C}_6\text{H}_4-\text{NH}-\text{CH}-\text{C}_6\text{H}_5 \\   \\ \text{CH}_2-\text{CO}-\text{R} \end{array}$	170-171	27	3.87, 3.83	3.57
IV	$\begin{array}{c} \text{p-H}_3\text{CO}-\text{C}_6\text{H}_4-\text{NH}-\text{CH}-\text{C}_6\text{H}_5 \\   \\ \text{CH}_2-\text{CO}-\text{R} \end{array}$	178-179	36	3.28, 3.30	3.43
V	$\begin{array}{c} \text{m-O}_2\text{N}-\text{C}_6\text{H}_4-\text{NH}-\text{CH}-\text{C}_6\text{H}_5 \\   \\ \text{CH}_2-\text{CO}-\text{R} \end{array}$	158-159	37	6.49, 6.36	6.62
VI	$\begin{array}{c} \text{p-Br}-\text{C}_6\text{H}_4-\text{NH}-\text{CH}-\text{C}_6\text{H}_5 \\   \\ \text{CH}_2-\text{CO}-\text{R} \end{array}$	134-135	40	2.93, 2.98	3.07
VII	$\begin{array}{c} \text{p-I}-\text{C}_6\text{H}_4-\text{NH}-\text{CH}-\text{C}_6\text{H}_5 \\   \\ \text{CH}_2-\text{CO}-\text{R} \end{array}$	183-184	42	2.73, 2.72	2.77
VIII	$\begin{array}{c} \text{C}_6\text{H}_5-\text{NH}-\text{CH}-\text{C}_6\text{H}_4-\text{CH}_3-\text{P} \\   \\ \text{CH}_2-\text{CO}-\text{R} \end{array}$	158-160	24	3.45, 3.34	3.57
IX	$\begin{array}{c} \text{P-CH}_3-\text{C}_6\text{H}_4-\text{NH}-\text{CH}-\text{C}_6\text{H}_4-\text{CH}_3-\text{P} \\   \\ \text{CH}_2-\text{CO}-\text{R} \end{array}$	155-156	32	3.20, 3.23	3.45
X	$\begin{array}{c} \text{m-CH}_3-\text{C}_6\text{H}_4-\text{NH}-\text{CH}-\text{C}_6\text{H}_4-\text{CH}_3-\text{P} \\   \\ \text{CH}_2-\text{CO}-\text{R} \end{array}$	149-150	26	3.22, 3.38	3.45
XI	$\begin{array}{c} \text{p-CH}_3\text{O}-\text{C}_6\text{H}_4-\text{NH}-\text{CH}-\text{C}_6\text{H}_4-\text{CH}_3-\text{P} \\   \\ \text{CH}_2-\text{CO}-\text{R} \end{array}$	142-143	34	3.09, 3.09	3.32
XII	$\begin{array}{c} \text{C}_6\text{H}_5-\text{NH}-\text{CH}-\text{C}_6\text{H}_4-\text{OCH}_3-\text{P} \\   \\ \text{CH}_2-\text{CO}-\text{R} \end{array}$	173-176	27	3.33, 3.33	3.43
XIII	$\begin{array}{c} \text{P-CH}_3-\text{C}_6\text{H}_4-\text{NH}-\text{CH}-\text{C}_6\text{H}_4-\text{OCH}_3-\text{P} \\   \\ \text{CH}_2-\text{CO}-\text{R} \end{array}$	157-158	30	3.16, 3.16	3.32
XIV	$\begin{array}{c} \text{m-CH}_3-\text{C}_6\text{H}_4-\text{NH}-\text{CH}-\text{C}_6\text{H}_4-\text{OCH}_3-\text{P} \\   \\ \text{CH}_2-\text{CO}-\text{R} \end{array}$	146-147	17	3.28, 3.42	3.32

The chalcones were also synthesized by a method [4] starting from methyl p-biphenyl ketone and benzaldehyde, p-tolualdehyde and anisaldehyde. The melting points of mixtures of the chalcones synthesized and those obtained by the hydramine cleavage showed no depression.

#### SUMMARY

The catalytic condensation of various Schiff's bases with methyl p-biphenyl ketone has been studied. Fourteen new  $\beta$ -arylamino ketones have been synthesized.

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# DERIVATIVES OF MORPHOLINE

## I. THE REACTION OF MORPHOLINE WITH 1,1,1-TRIS (CHLOROMETHYL) PROPANE AND WITH THE TRICHLOROHYDRIN OF PENTAERYTHRITOL

S. Z. Kaplan and A. S. Zvontsova

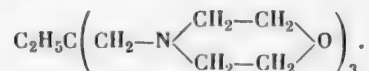
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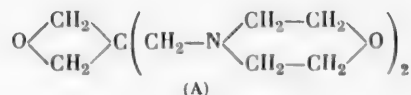
It is known that N-alkylmorpholines can be prepared by the condensation of alkyl halides with an excess of morpholine [1]. In order to obtain derivatives of morpholine containing several morpholine rings in the molecule, morpholine was condensed with 1,1,1-tris (chloromethyl) propane (I) and the trichlorohydrin of pentaerythritol (II). The morpholine was used in 2-fold excess to tie up the hydrogen chloride.

It might be assumed that the nucleophilic substitution of chlorine in  $C_2H_5C(CH_2Cl)_3$  would go very slowly, both as a type  $S_N1$  reaction as a result of the difficulty of ionization of the chlorine and as a type  $S_N2$  reaction because of the steric hindrances. This follows from a comparison of the structure of 1,1,1-tris(chloromethyl)propane with a number of compounds of similar structure whose reactivity is known [2]. Actually, the reaction of 1,1,1-tris(chloromethyl)propane with morpholine does not go at 130-140° even on 44 hours' heating. We succeeded in carrying out the condensation by heating the reaction mixture in sealed tubes at 180-200°, during which process a compound was formed that according to its analysis had the following structure:

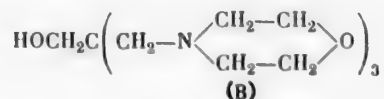


The second compound used for condensation with morpholine,  $HOCH_2C(CH_2Cl)_3$ , was more reactive because of the presence of the hydroxyl group. Here the formation of intermediate cyclic products is possible as a result of the unshared electron pair of the oxygen atom, and this should facilitate the substitution of chlorine [3]. Actually, when morpholine was heated for 12 hours with trichlorohydrin of pentaerythritol at 180-200°, the condensation product was obtained in 72% yield.

Similarly, we might expect the formation of compound (A) by the reaction of the tribromohydrin of pentaerythritol with ammonia [4].



Analysis of the reaction product showed, however, that the compound of structure (B) was obtained.



The hydroxyl group was determined in it by the method of Verley and Belsing [5].

## EXPERIMENTAL

1,1,1-Tris (chloromethyl) propane was prepared by the reaction of ethyltrimethylolmethane with thionyl chloride by analogy with the data in reference [6]. Its properties agreed with those in the literature [7]. The trichlorohydrin of pentaerythritol had the m.p. 60°; according to the literature the m.p. is 65.5° [6].

Reaction of 1,1,1-tris (chloromethyl) propane with morpholine. A mixture of 9 g of morpholine and 3 g of the halogen compound was heated in a sealed tube at 180-200° for 12 hours. A brown liquid with a precipitate formed in the ampoule (sometimes the precipitate separated out when the ampoule was shaken). It was diluted with ether. The insoluble morpholine salt was filtered off. The ether solution was dried with potassium hydroxide and after the solvent had been distilled off, the residue was distilled in vacuum. Morpholine and 1,1,1-tris (chloromethyl) propane distilled below 100° (4 mm), and then the condensation product distilled at 168-170° (4 mm). Distillation was continued on a Wood's metal bath. At 220° (2 mm), white vapors of decomposition appeared and several drops of material distilled off with  $n_D^{17}$  1.4760. The residue in the flask was not investigated. The amount of reaction product obtained was 0.47 g. The yield depended on the time of heating and was 8.7% in 12 hours, 17.4% in 24 hours (calculated on the basis of the trichlorohydrin used for the reaction).

1,1,1-Tris (morpholinomethyl) propane was a white compound with m.p. 105-106° (from alcohol).

Found %: C 64.03, 63.82; H 10.61, 10.49; N 12.34, 12.56. M 335.8.  $C_{18}H_{35}O_3N_3$ . Calculated %: C 63.30; H 10.33; N 12.30, M 341.49.

It dissolved readily in benzene and on heating in methyl and ethyl alcohols, was slightly soluble in cold water, and showed an alkaline reaction to phenolphthalein.

Hydrobromide: m.p. 225° (decomp).

Picrate: m.p. 207-209° (from water, with decomp).

Found %: N 15.94, 15.98.  $C_{18}H_{35}O_3N_3 \cdot 3C_6H_5(NO_2)_2OH$ . Calculated %: N 16.34.

Picolonate: m.p. 206-207° (from alcohol).

Reaction of trichlorohydrin of pentaerythritol with morphine. When 9 g of morpholine was heated with 3 g of the trichlorohydrin of pentaerythritol for 12 hours in a sealed tube at 180-200°, a light brown solid mass was formed. It was transferred to a filter and washed with ether, and then with cold water to remove chloride ions. From the ethereal filtrate 0.17 g was isolated, and 1.80 g of white, finely crystalline material remained on the filter. The combined aqueous extracts were evaporated to dryness on a water bath, the residue was made alkaline with 40% KOH (to phenolphthalein), filtered off, and washed free of chloride ions. An additional 1.82 g of material was obtained which did not give a depression in melting point when mixed with the first precipitate. M.p. 184-185° (from benzene).

Found %: C 60.17, 59.93; H 9.86, 9.96; N 12.32, 12.29. M 331. Equiv. (for one OH group) 323.  $C_{17}H_{33}O_4N_3$ . Calculated %: C 59.43; H 9.68; N 12.23. M 343.49. Equiv. 343.49.

Methyloltrimorpholinomethylmethane was slightly soluble in cold water, had an alkaline reaction, dissolved on heating in benzene, methyl and ethyl alcohols, and was more difficultly soluble in acetone and ethyl acetate.

Picolonate: m.p. 205° (from alcohol).

## SUMMARY

Morpholine has been condensed with 1,1,1-tris (chloromethyl) propane and with the trichlorohydrin of pentaerythritol for the first time.

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# INVESTIGATION IN THE FIELD OF ALKANESULFONIC ACIDS

## XXIV. ACETYLATION OF SOME ALKANESULFO-N-ARYLAMIDES IN THE PRESENCE OF ALUMINUM CHLORIDE

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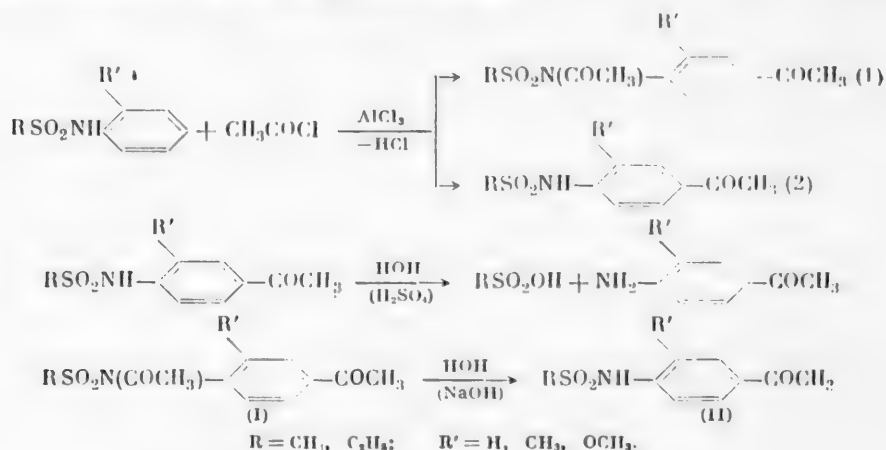
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It is known that acylation of alkanesulfo-N-arylamides without a catalyst leads, as a rule, to the N-acyl derivatives [1].

In the present work we have studied the acetylation of some N-arylamides in the presence of  $\text{AlCl}_3$  in solution in dichloroethane, which, as it turned out, does not react with the benzene nucleus under the conditions employed. The anilides, o-toluidides and o-anisidides of methane and ethanesulfonic acids were used for the reaction. It was shown that the reaction proceeds with the formation of two ketones, one acetylated in the nucleus and on the nitrogen, which for the sake of brevity will be further referred to as the diacetyl derivative (I), and the other acetylated only in the nucleus, referred to as the monoacetyl derivative (II). (I) was insoluble and (II) was soluble in dilute alkali, which was used to separate them. When the anilides and o-toluidides of methanesulfonic acid were acetylated, (II) was formed in larger yield, but for these same derivatives of ethanesulfonic acid the opposite was true. In the case of the o-anisidides, (II) was predominantly formed and (I) was isolated in low yield, especially the ethanesulfo derivative. It was shown through the example of methanesulfo-o-toluidide that the yields of the two products depend on the amount of acetyl chloride used: with an increase in the amount of the latter the yield of (I) was increased and that of (II) was decreased. The duration of the reaction (from 3 to 5 hours) did not have a substantial effect on the quantitative ratio of the products. (I) was easily hydrolyzed on slight heating in dilute alkali, being converted to (II) by this process; the acetyl group in the o-anisidide derivatives was the most easily split off, and that in the anilide derivatives with more difficulty. The acetyl group entered the benzene ring in the para position to the alkylsulfamido group, as indicated by hydrolysis by dilute sulfuric acid of the ketones obtained to the corresponding substituted acetophenones. The p-toluidides and p-anisidides were not acetylated. All the reactions that have been enumerated can be expressed by the following general schemes.



As can be seen from equation (1), the compounds obtained were alkanesulfo derivatives of various p-aminoacetophenones. These were slightly yellowish crystalline compounds with rather high melting points in comparison with the starting N-aryl amides and their N-acetyl derivatives.

TABLE I

No.	Formula of compound	Name	Initial amount, g			Yield		M. p.		% N		% S	
			N-arylamide	acetyl chloride	aluminum chloride	g	%			found	calc.	found	calc.
1	$\text{CH}_3\text{SO}_2\text{NH}-\text{C}_6\text{H}_4-\text{COCH}_3$ ( $\text{C}_{11}\text{H}_{11}\text{O}_3\text{NS}$ )	Methanesulfo-4-acetanilide	1.0	1.01	2.35	0.34	28.0	150—152°		6.42	6.57	14.95	15.02
2	$\text{CH}_3\text{SO}_2\text{N}-\text{C}_6\text{H}_4-\text{COCH}_3$ $\text{COCH}_3$ ( $\text{C}_{11}\text{H}_{11}\text{O}_3\text{NS}$ )	Methanesulfo-N-acetyl-4-acetanilide				0.6	40.3	132—133		5.50	5.49	12.60	12.54
3	$\text{C}_7\text{H}_5\text{SO}_2\text{NH}-\text{C}_6\text{H}_4-\text{COCH}_3$ ( $\text{C}_{10}\text{H}_{10}\text{O}_3\text{NS}$ )	Ethanesulfo-4-acetanilide	1.5	1.36	3.24	1.1	57.12	130—132		6.01	6.16	14.20	14.10
4	$\text{C}_7\text{H}_5\text{SO}_2\text{N}-\text{C}_6\text{H}_4-\text{COCH}_3$ $\text{COCH}_3$ ( $\text{C}_{10}\text{H}_{10}\text{O}_3\text{NS}$ )	Ethanesulfo-N-acetyl-4-acetanilide				0.44	19.9	94—96		5.10	5.20	12.08	11.89
5	$\text{CH}_3\text{SO}_2\text{NH}-\text{C}_6\text{H}_3(\text{CH}_3)-\text{COCH}_3$ $\text{CH}_3$ ( $\text{C}_{10}\text{H}_9\text{O}_3\text{NS}$ )	Methanesulfo-5-aceto-o-toluidide				1.1	61.1	150—151		6.20	6.16	14.03	14.10
6	$\text{CH}_3\text{SO}_2\text{N}-\text{C}_6\text{H}_3(\text{CH}_3)-\text{COCH}_3$ $\text{COCH}_3$ $\text{CH}_3$ ( $\text{C}_{11}\text{H}_9\text{O}_3\text{NS}$ )	Methanesulfo-N-acetyl-o-toluidide	1.5	0.97	3.15	0.21	9.6	162—163		5.05	5.20	11.81	11.89

(continued on next page)

TABLE 1 (continued)

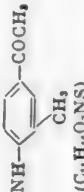
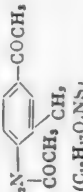
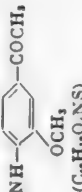
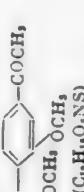
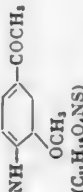
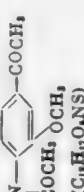
No.	Formula of compound	Name	Initial amount, g			Yield		M. p.	% N		% S	
			N-arylam- ide	acetyl chlo- ride	aluminum chloride	g	%		found	calc.	found	calc.
7	 $C_6H_4SO_3NH-CH_2-COCH_3$ ( $C_{11}H_{13}O_3NS$ )	Ethanesulfo-5-acetyl- o-toluidide	2.0	1.4	4.12	0.6	25.0	124—126°	5.64	5.80	13.15	13.27
8	 $C_6H_4SO_3N-CH_2-COCH_3$ ( $C_{12}H_{13}O_3NS$ )	Ethanesulfo-N-acetyl- 5-acetyl-o-toluidide				1.07	44.6	114—115	5.07	4.93	11.67	11.30
9	 $CH_3SO_3NH-CH_2-COCH_3$ ( $C_{12}H_{13}O_3NS$ )	Methanesulfo-5-acetyl- o-anisidide	2.5	2.16	5.0	0.4	13.12	140—141	5.72	5.76	13.45	13.16
10	 $CH_3SO_3N-CH_2-COCH_3$ ( $C_{12}H_{13}O_3NS$ )	Methanesulfo-N-acetyl- 5-acetyl-o-anisidide				1.9	53.37	165—167	5.08	4.91	11.24	11.22
11	 $C_6H_4SO_3NH-CH_2-COCH_3$ ( $C_{11}H_{13}O_3NS$ )	Ethanesulfo-5-acetyl- o-anisidide	1.7	1.3	3.14	Следы		116—117	5.49	5.44	12.51	12.45
12	 $C_6H_4SO_3N-CH_2-COCH_3$ ( $C_{12}H_{13}O_3NS$ )	Ethanesulfo-N-acetyl- 5-o-anisidide				1.31	43.0	155—156	4.51	4.68	10.57	10.70

TABLE 2



No.	Used for reaction, g			Molar proportions	Yields of reaction products			
	tolu- idide	AlCl <sub>3</sub>	CH <sub>3</sub> COCl		<div>CH<sub>3</sub>SO<sub>2</sub>NH-COCH<sub>3</sub></div>		<div>CH<sub>3</sub>SO<sub>2</sub>N(COCH<sub>3</sub>)-COCH<sub>3</sub></div>	
					g	%	g	%
1	1.5	3.15	0.97	1 : 3 : 1.5	1.1	61.1	0.21	9.6
2	2.5	3.15	1.27	1 : 3 : 2	0.9	50.0	0.57	26.03
3	1.5	3.15	1.9	1 : 3 : 3	0.78	42.3	0.72	32.7

TABLE 3

No.	Hydrolyzed compound	Used for hydrolysis, g	Hydrolysis time, min	Yield of hydrolysis product	
				g	%
1	$\text{CH}_3\text{SO}_2\text{N}(\text{COCH}_3)-\text{C}_6\text{H}_4-\text{COCH}_3$	0.2	5	0.12	75.0
2	$\text{C}_2\text{H}_5\text{SO}_2\text{N}(\text{COCH}_3)-\text{C}_6\text{H}_4-\text{COCH}_3$	0.3	5	0.22	86.47
3	$\text{CH}_3\text{SO}_2\text{N}(\text{COCH}_3)-\text{C}_6\text{H}_3(\text{CH}_3)-\text{COCH}_3$	0.3	2-3	0.21	83.0
4	$\text{C}_2\text{H}_5\text{SO}_2\text{N}(\text{COCH}_3)-\text{C}_6\text{H}_3(\text{CH}_3)-\text{COCH}_3$	0.2	2-3	0.14	82.3
5	$\text{CH}_3\text{SO}_2\text{N}(\text{COCH}_3)-\text{C}_6\text{H}_3(\text{OCH}_3)-\text{COCH}_3$	0.3	1	0.2	80.0
6	$\text{C}_2\text{H}_5\text{SO}_2\text{N}(\text{COCH}_3)-\text{C}_6\text{H}_3(\text{OCH}_3)_2-\text{COCH}_3$	0.2	1-2	0.13	76.47

## EXPERIMENTAL

The reaction in all cases was carried out by the following method. The starting compounds—N-arylamide, acetyl chloride and aluminum chloride—were used in the proportions 1: 2: 3, respectively. The calculated amounts of the N-arylamide and aluminum chloride were placed in a round-bottomed flask fitted with a two-branched adapter, a dropping funnel and a condenser. To the mixture was added dry dichloroethane (20 ml), and then the acetyl chloride was added gradually from the dropping funnel with cooling. The mixture was left for 1 hour at ~20°, then was heated for 3-5 hours on a water bath at a temperature not above 50°. At the end of the reaction the contents of the flask were treated with ice water acidified with hydrochloric acid. The dichloroethane layer was separated, washed twice with water, and left in a porcelain dish for the dichloroethane to evaporate. The remaining solid product was treated with 5% alkali solution. In this process the monoacetyl derivative (II) dissolved in the alkali and was isolated by acidification of the alkaline solution in the form of a crystalline precipitate; the diacetyl derivative (I) was insoluble in alkali. Both products were recrystallized from aqueous alcohol or aqueous acetone. The results of the experiments, the constants and the data from the analyses of the compounds obtained are given in Table 1.

In the case of the o-toluidide of methanesulfonic acid the experiments were carried out with one and a half, two and three times the amount of acetyl chloride relative to the o-toluidide under otherwise equal conditions. The results are given in Table 2.

Demonstration of structure of ketones by hydrolysis. Methanesulfo-4-acetanilide and methanesulfo-5-aceto-o-toluidide were used for the reaction in the amount of 0.5 g in 10 ml of dilute (1: 1) sulfuric acid. The hydrolysis was carried out by a previously described method [1]. From the acetanilide, 4-aminoacetophenone was isolated with m.p. 104-106° (from hot water); according to data in the literature [2] m.p. 106°. From the aceto-o-toluidide was isolated 3-methyl-4-aminoacetophenone with m.p. 105°; according to data in the literature [2] m.p. 102°. Analyses for nitrogen also corresponded to the compounds. The structure was not demonstrated for the anisidides.

Found %: N 10.22.  $C_8H_9ON$ . Calculated %: N 10.36.

Found %: N 9.33.  $C_9H_{11}ON$ . Calculated %: N 9.39.

Hydrolysis of N-acetylketones (I) with dilute alkali. Hydrolysis with 5% alkali solution was carried out by heating on a water bath until the precipitate dissolved completely in the alkali. On acidification of the alkaline solution the corresponding compound (II) precipitated. Mixed melting point tests of the products obtained by reaction and by hydrolysis gave no depression. The data for the hydrolysis are given in Table 3.

#### SUMMARY

1. The acetylation of several alkanesulfo-N-arylamides in the presence of aluminum chloride has been studied. It has been shown that in all cases the reaction proceeds with the formation of two ketones, acetylated and unacetylated on the nitrogen, the quantitative ratio of which depends on the amount of acetyl chloride, but does not depend on the reaction time.

2. It was demonstrated by hydrolysis that the acetyl group enters the ring in the para position to the alkylsulfamido group. It has been shown that the acetyl group on the nitrogen is easily split off by the action of dilute alkali.

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2. *Beilst.* XIV, 64, 46 (1931).

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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# REACTION OF ACRYLONITRILE WITH DIPHENYL

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The reaction of acrylonitrile with diphenyl has not been described. There are patent data [1] on the reaction of benzene with acrylonitrile or acrylic acid which indicate the possibility of obtaining a fatty-aromatic nitrile or the corresponding acid. At the same time the passivity of acrylonitrile with respect to aromatic compounds, particularly benzene, is recorded in the literature [2]. A. D. Grebenyuk and I. P. Tsukervanik [3] have shown that under severe reaction conditions (140-180°, pressure) the stability of the complex of acrylonitrile with aluminum chloride decreases, which facilitates the preparation of fatty-aromatic nitriles in small yield.

The purpose of the present investigation was the study of the reaction of diphenyl with acrylonitrile in the presence of aluminum chloride.

## EXPERIMENTAL

Cyanoethylation of diphenyl. Experiments on the cyanoethylation of diphenyl by acrylonitrile at atmospheric pressure in carbon tetrachloride solution in the presence of hydrogen chloride or directly by  $\beta$ -chloropropionitrile led to the formation mainly of the hydrocarbon bis (1,2-diphenyl)-ethane with m.p. 196-205° (according to literature data [4] m.p. 198-205°) and a powdery resin insoluble in the usual organic solvents.

The results of experiments on the reaction of diphenyl with acrylonitrile carried out in a stainless steel autoclave in the presence of anhydrous aluminum chloride at 164-170° for 8 hours with different proportions of the starting materials are given in the table. To avoid concurrent complex formation between the acrylonitrile and the aluminum chloride the reagents were added in the following order: part of the diphenyl was mixed in the autoclave with the acrylonitrile; the diluted remainder of the diphenyl and then the aluminum chloride were added to the mixture obtained.

Cyanoethylation of Diphenyl

Ratio of Reagents			Yield of Mono-nitrile (%)	Amount		Nature of Reaction Product
Diphenyl	Acrylonitrile	Aluminum Chloride		Resinous Residue (in %)	Diphenyl Recovered (in %)	
3	1	3.5	36.0	39.0	25.0	Viscous
2	1	3.5	18.8	54.2	27.0	Viscous
3	1	1	13.9	16.1	70.0	Solid

From the data in the table it is seen that the largest yield of the main product (36%) was obtained with a diphenyl: acrylonitrile: aluminum chloride ratio of 3: 1: 3.5, respectively.

Isolation and identification of products of cyanoethylation of diphenyl. The crude reaction product was transferred in small portions to a beaker with 10% hydrochloric acid solution, cooled with ice so that the temperature of the decomposition mass did not exceed 20-25°. The aqueous acid layer was separated by decantation from the resin sticking to the beaker and was extracted with carbon tetrachloride. About 150 g of resin was treated with 4 liters of carbon tetrachloride, whereupon ~120 g of the resin went into solution. The combined extract was washed with water and hydrochloric acid to remove the aluminum salts, dried over calcium chloride, and then filtered. The solvent was distilled off on a water bath and the residue was distilled in vacuum (1 mm). The following fractions were separated:

1st 90-92° (1 mm), diphenyl; 2nd liquid material:

B.p. 145-148° (1 mm),  $n_D^{20}$  1.580,  $d_4^{20}$  1.071,  $MR_D$  64.32.  $C_{15}H_{13}N$ . Calculated 63.846 (taking into account the exaltation for the two benzene rings, equal to 0.24).



3rd fraction, a waxy material, b.p. 163-165° (1 mm). When recrystallized once from methanol it became crystalline with m.p. 89.5-90°.

Found %: C 86.46; H 6.31; N 6.57, 6.88.  $C_{15}H_{13}N$ . Calculated %: C 86.91; H 6.32; N 6.75.

4th fraction, a viscous oil, b.p. 192-250° (1 mm) (with decomp.), partially steam-distilled. From 2.8 g of this fraction was isolated 0.5 g of a thick oil, treatment of which with alkali and prolonged heating did not lead to the formation of an acid.

4-Diphenylpropionic acid. One gram of crystalline 4-diphenylpropionitrile (p-phenylhydrocinnamionitrile) from fraction 3 was heated with 40 ml of 10% sodium hydroxide solution for 5 hours in a flask with a reflux condenser with vigorous stirring. The salt of the acid which was formed was difficultly soluble in water. To dissolve it the mixture was diluted with 100 ml of water and heated for 2.5 hours, then filtered. The still warm filtrate was acidified with concentrated hydrochloric acid with stirring. Yield 1.09 g (99%). M.p. 145-146° (from water). According to the literature data m.p. 145° [5].

2-Diphenylpropionic acid. Four grams of the waxy product from fraction 3 was subjected to alkaline hydrolysis with 160 ml of 10% sodium hydroxide solution. To dissolve the sodium salt, which was obtained in the form of a precipitate, the mixture was diluted with 150 ml of hot water, boiled for 2.5 hours, and filtered from the sediment. The filtrate was acidified with concentrated hydrochloric acid with stirring. The crystals that precipitated were filtered off, washed with water to remove mineral acid and salts, and dried in vacuum over phosphoric anhydride. Yield 2.3 g (55%), m.p. 88-95°.

The compound (2.3 g) was dissolved in 80 ml of 10% sodium carbonate solution. The colored sodium carbonate solution was boiled with 0.5 g of activated carbon and the hot solution was filtered. After acidification of the filtrate, washing of the precipitated crystals with water, and drying in vacuum over phosphoric anhydride, the compound was obtained with m.p. 110-111° (from 81% methanol).

Found %: C 79.90; H 6.29.  $C_{15}H_{14}O_2$ . Calculated %: C 79.64; H 6.19.

One gram of this compound was oxidized with 10 ml of 20% nitric acid by heating in a flask with a reflux condenser, mechanical stirrer and thermometer at 120-140° for 2 hours. On cooling of the mixture, crystals precipitated. The acid solution was diluted with an equal volume of water. The oxidation product was filtered off and washed with water. M.p. 108-110° (from water). According to data in the literature the m.p. for the 2-diphenylcarboxylic acid is 111° [6]. The neutralization equivalents found were 198 and 197.5; the calculated equivalent was 198. A mixed sample of the starting acid and the oxidation product gave a depression in melting point.

#### SUMMARY

1. The cyanoethylation of diphenyl in the presence of aluminum chloride has been investigated.
2. It has been shown that as a result of the reaction of diphenyl, acrylonitrile and aluminum chloride in the proportions 3: 1: 3.5 is a mixture produced of the 2- and 4-isomers of diphenylisopropionitrile, which have not been described in the literature, with a 36% yield of crude product.
3. By hydrolysis of the corresponding nitriles, the 2- and 4-diphenylpropionic acids were obtained and identified.

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5. Beilst. 9 (287).
6. Beilst. 9 (279).

# SYNTHESIS OF OXYGENEOUS ALIPHATIC DISULFIDES

S. M. Gurvich

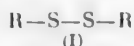
State Scientific Research Institute for Nonferrous Metals

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We undertook the synthesis of various nonferrous oxygenous disulfides (I) in our search for flotation agents—collectors for the flotation of so-called "cement" copper (copper precipitated by iron from sulfuric acid solutions).



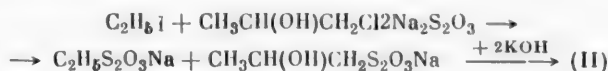
R = CH<sub>3</sub>OCH<sub>2</sub>CH(CH<sub>3</sub>) (a); (CH<sub>3</sub>)<sub>2</sub>CHOCH<sub>2</sub>CH(CH<sub>3</sub>) (b); C<sub>2</sub>H<sub>5</sub>OCH<sub>2</sub> (c); n-C<sub>3</sub>H<sub>7</sub>OCH<sub>2</sub> (d);  
ClCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub> (e); CH<sub>3</sub>COOCH<sub>2</sub>CH<sub>2</sub> (f); n-C<sub>2</sub>H<sub>5</sub>COOCH<sub>2</sub>CH<sub>2</sub> (g); CH<sub>3</sub>CH(OH)CH<sub>2</sub> (h);  
CH<sub>3</sub>CH(OCOCH<sub>3</sub>)CH<sub>2</sub> (i); CH<sub>3</sub>CH(OCOC<sub>2</sub>H<sub>5</sub>-n)CH<sub>2</sub> (j); HOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub> (k).

The disulfides were synthesized by boiling the corresponding chlorides with a small excess of 2-2.5 M aqueous sodium disulfide solution. These conditions of the synthesis favor a side reaction, i.e., the hydrolysis of the initial chlorides (the mixture has a pH = 10-11), which obviously is the main reason for the relatively low yields of disulfides (20-45%).

The initial chloro ethers were obtained from the corresponding hydroxy ethers. 2-Ethoxyethyl chloride and 1-methoxy-2-chloropropane were synthesized by the interaction with cellosolve [1] of thionyl chloride and the mono-methyl ether of propylene glycol, respectively. Analogously, 1-isopropoxy-2-chloropropane was obtained by the action of phosphorus trichloride on monoisopropyl ether of propylene glycol. The chloromethyl alkyl ethers were prepared by standard methods [2]. The chlorohydrins of ethylene glycol and propylene glycol were prepared by reaction of the corresponding oxides with gaseous hydrogen chloride—in the vapor phase, and with concentrated hydrochloric acid—in the liquid phase, respectively. The 2-chloro-2-hydroxyethyl ether was prepared by the action of phosphorus trichloride on an excess of diethylene glycol. The disulfides (Ia-d) were synthesized by typical methods. During the reaction of chlorex (2,2'-dichlorodiethyl ether) with sodium disulfide, the latter solution was slowly added to a double excess of chlorex for better suppression of a side reaction, namely, polycondensation of the thiocol type which leads to the formation of high-molecular polydisulfide. The dithiodiethyleneglycol is well-known [3], but its diacetyl (If) and dibutyl (Ig) derivatives are not described and were obtained by us for the first time. Analogously, dithiodipropylene glycol (Ih) was prepared from propylene chlorohydrin, as well as its diacetyl (Ii) and dibutyl (Ij) derivatives. The di[2-(2'-hydroxyethoxy)ethyl] disulfide (Ik), containing oxygen simultaneously in two different functions, was prepared by a typical reaction from 2-chloro-2'-hydroxydiethyl ether. An unsymmetrical disulfide was also synthesized, i.e., ethyl-2-hydroxypropyl disulfide (II). First, by means of sodium disulfide:



second, by means of sodium thiosulfate:



and finally, by redistribution of disulfides [4]:



The last reaction occurs in the presence of sodium disulfide, and here is it recommended for faster equilibrium attainment to use Nekal (sodium salt of butylnaphthalene-sulfonic acid) as an emulsifier, and for increasing the surface reactivity under the heterogeneous condition, the use of freshly precipitated magnesium oxide.

The flotation studies of the disulfides described here showed that best results were obtained with di(1-methyl-2-methoxyethyl) disulfide and di[2-(2'-chloroethoxy)ethyl] disulfide [5].

The author thanks A. K. Livshits for the care given to this work.

#### EXPERIMENTAL

Di(1-methyl-2-methoxyethyl) disulfide (Ia). A mixture of 19.5 ml of a 2.56 M solution (0.05 mole) sodium disulfide and 10.85 g (0.1 mole) 1-methoxy-2-chloropropane [6] was agitated for 7 hours at 80°; the upper layer was dissolved in ether, the lower one was worked up with ether (4 times 25 ml), the ether extracts combined with the ether solution, washed with water, and dried with magnesium sulfate. Yield: 2.7 g (26%).

B.p. 77-79° (1 mm),  $d_4^{20}$  1.0414,  $n_D^{20}$  1.4940,  $MR_D$  58.89. Calculated 58.65.

Found %: C 45.42, 45.49; H 8.55, 8.81; S 30.54, 30.69.  $C_8H_{18}O_2S_2$ . Calculated %: C 45.67; H 8.64; S 30.48.

Di(1-methyl-2-isopropoxyethyl) disulfide (Ib). A 2.56 M solution (0.042 mole) as 15.7 ml sodium disulfide and 11.1 g (0.082 mole) of 1-isopropoxy-2-chloropropane [7] was boiled for 8 hours, and 2.4 g disulfide (Ib) was isolated.

B.p. 83-84.5° (0.45 mm),  $d_4^{20}$  0.9725,  $n_D^{20}$  1.4769,  $MR_D$  77.30. Calculated 77.12.

Found %: C 53.57, 53.83; H 9.82, 9.76; S 24.07, 24.09.  $C_{12}H_{26}O_2S_2$ . Calculated %: C 54.09, H 9.83; S 24.07.

Di(ethoxymethyl) disulfide (Ic). Analogously, 97 ml of a 2.56 M solution (0.25 mole) sodium disulfide and 47.25 g (0.5 mole) chloromethyl ethyl ether [8] gave 4.9 g disulfide (Ic).

B.p. 64-64.5° (1 mm),  $d_4^{20}$  1.0822,  $n_D^{20}$  1.4979,  $MR_D$  49.37. Calculated 49.41.

Found %: S 35.11, 34.89.  $C_6H_{14}O_2S_2$ . Calculated %: S 35.18.

Di(n-propoxymethyl) disulfide (Id). Analogously, 97 ml 2.56 M solution (0.25 mole) of sodium disulfide and 54.25 g (0.5 mole) chloromethyl propyl ether [9] gave 4.15 g disulfide (Id).

B.p. 70-73° (0.35 mm),  $d_4^{20}$  1.0392,  $n_D^{20}$  1.4893,  $MR_D$  58.46. Calculated 58.65.

Found %: S 30.12, 30.33.  $C_8H_{18}O_2S_2$ . Calculated %: S 30.49.

Di[2-(2'-chloroethoxy)ethyl] disulfide (Ie). To a boiling solution of 114.4 g (0.8 mole) of chlorex in 80 ml methanol was added, over a period of two hours, 78 ml of 2.56 M solution (0.2 mole) sodium disulfide, the mixture boiled for four hours (the mixture changed from orange to light yellow), the methanol distilled off, the remainder filtered, the organic layer separated, and from the latter the excess chlorex distilled in vacuo (20 mm); the yield of unpurified disulfide was 29.4 g (52.8%). A light yellow liquid was obtained after two more distillations.

B.p. 142-147° (0.53 mm),  $d_4^{20}$  1.3062,  $n_D^{20}$  1.5685.

Found %: S 22.71, 22.57; Cl 25.60, 25.77.  $C_8H_{16}O_2S_2Cl_2$ . Calculated %: S 22.96; Cl 25.39.

Dithiodiethylene glycol diacetate (If). To 5 g dithiodiethylene glycol [3] was added, under cooling and slowly, 15.3 g acetyl chloride, the mixture boiled for one hour, the excess acetyl chloride vacuum distilled, and the rest twice distilled. Yield: 5.0 g (65.5%).

B.p. 114-115° (0.55 mm),  $d_4^{20}$  1.2053,  $n_D^{20}$  1.5022,  $MR_D$  58.35. Calculated 58.67.

Dithiodiethylene glycol dibutyrate (Ig). Analogously, 5 g dithiodiethylene glycol and 20.73 g butyryl chloride (2-hour boiling) gave 5.14 g (54%) (Ig).

B.p. 135-137° (0.45 mm),  $d_4^{20}$  1.1064,  $n_D^{20}$  1.4892,  $MR_D$  76.83. Calculated 77.14.

Dithiodipropylene glycol (Ih). Analogously, to the synthesis of dithiodiethylene glycol, 162 ml of 2.5 M solution (0.405 mole) sodium disulfide and 70 g (0.75 mole) propylene chlorohydrin [10] gave 53.4 g (78%) unpurified substance, from which the glycol (Ih) was obtained after two distillations.

B.p. 117-119° (0.55 mm),  $d_4^{20}$  1.1796,  $n_D^{20}$  1.5468,  $MR_D$  48.89. Calculated 49.18.

Found %: C 40.01, 39.79; H 7.70, 7.59; S 35.07, 35.12.  $C_6H_{14}O_2S_2$ . Calculated %: C 39.53; H 7.74; S 35.18.

Diacetate (Ii). Dithiodipropylene glycol (5 g) and 12.96 g acetyl chloride gave, analogously to (If), (Ii); yield: 2.4 g (39.4%).

B.p. 96-98° (0.6 mm),  $d_4^{20}$  1.1703,  $n_D^{20}$  1.5075,  $MR_D$  67.70. Calculated 67.91.

Dibutyrate (Ij). Dithiodipropylene glycol (5 g) and 17.55 g butyryl chloride analogously to (Ig) gave (Ij); yield: 4.7 g (57%).

B.p. 133-137° (0.5 mm),  $d_4^{20}$  1.0722,  $n_D^{20}$  1.4830,  $MR_D$  85.76. Calculated 85.24.

Di[2-(2'-hydroxyethoxy)ethyl] disulfide (Ik). A mixture of 37 ml 2.5 M solution (0.092 mole) sodium disulfide and 20.9 g (0.167 mole) 2-chloro-2'-hydroxydiethyl ether [11] was heated at 60-70° for three hours, the organic layer separated, dried with magnesium sulfate, and vacuum distilled. Yield: 3.7 g.

B.p. 161-165° (0.5 mm),  $d_4^{20}$  1.2074,  $n_D^{20}$  1.5218,  $MR_D$  61.20. Calculated 61.70.

Found %: C 40.09, 39.86; H 7.53, 7.65.  $C_8H_{18}O_4S_2$ . Calculated %: C 39.64; H 7.49.

Ethyl-2-hydroxypropyl disulfide (II). a) A mixture of 274 ml of 2.73 M solution (0.75 mole) sodium disulfide, 47.25 g (0.5 mole) propylene chlorohydrin and 78 g (0.5 mole) ethyl iodide was heated at 100° for two hours, cooled, and the upper oily layer separated; the aqueous layer was extracted with ether (6 times 25 ml). The ether extracts were combined with the main layer and dried with magnesium sulfate; the ether was distilled off and two more distillations gave 10.36 g disulfide (II).

B.p. 64-68° (1 mm),  $d_4^{20}$  1.0928,  $n_D^{20}$  1.5283,  $MR_D$  42.98. Calculated 43.03.

Found %: C 39.29, 39.34; H 7.79, 8.00.  $C_5H_{12}OS_2$ . Calculated %: C 39.43; H 7.94.

b) Propylene chlorohydrin (47.25 g, 0.5 mole), 78 g (0.5 mole) ethyl iodide, 550 g (2 mole) sodium thiosulfate, 850 ml water and 750 ml methanol were mixed for six hours at 80°, 203.7 g potassium hydroxide in 440 ml water added to it, and all was heated for one more hour, and this in the usual manner gave 2.4 g (II).

c) A mixture of 84 ml 1.82 M solution of sodium disulfide in methanol, 70 ml methanol, 3.2 ml 1% Nkal solution, 4 ml 10% caustic soda solution, 1.9 ml 25% solution of magnesium chloride, 7 g (0.038 mole) dithiopropylene glycol and 4.64 g (0.038 mole) diethyldisulfide was heated under stirring for 11 hours. After removal of methanol by distillation, the residue was extracted with ether, the extract dried with magnesium sulfate, the ether distilled off, and 1.6 g disulfide was isolated from the residue.

#### SUMMARY

1. For the first time eleven symmetrical oxygeneous aliphatic disulfides were synthesized by a reaction of the corresponding chlorides with sodium disulfide.
2. Ethyl-2-hydroxypropyl disulfide, previously unknown, was obtained by three different methods.
3. Di(1-methyl-2-methoxyethyl)- and di[2-(2'-chloroethoxy)ethyl] disulfides are of interest as reagents-collectors for the flotation of cement copper.

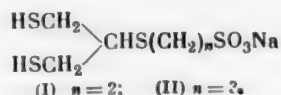
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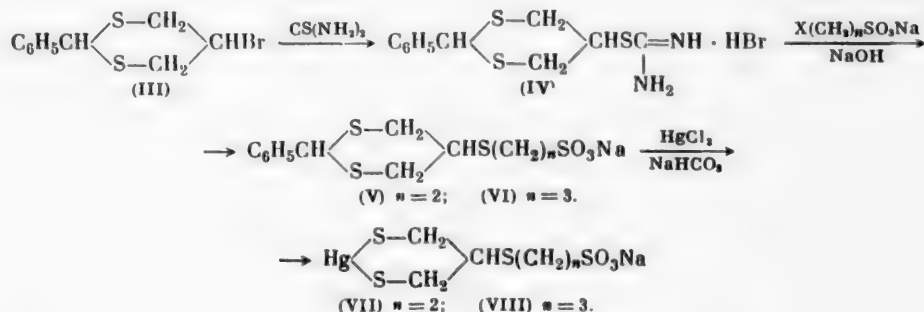
VI. 2-( $\beta,\beta'$ -DIMERCAPTOISOPROPYLMERCAPTO)ETHANE- AND 3-( $\beta,\beta'$ -DIMERCAPTOISOPROPYLMERCAPTO)PROPANE SODIUM SULFONATE\*

Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 7,  
pp. 2252-2255, July, 1961  
Original article submitted August 3, 1959

Cleavage of the dithiane ring of the corresponding 1,3-dithiane derivatives by mercuric chloride was successfully applied to the synthesis of sodium 2-( $\beta$ , $\beta'$ -dimercaptoisopropylmercapto)ethane sulfonate (I) and 3-( $\beta$ , $\beta'$ -dimercaptoisopropylmercapto)propane sulfonate (II).

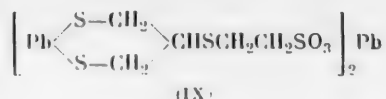


2-Phenyl-1,3-dithiane-5-isothiuronyl bromide (IV) was prepared by the condensation of previously described [2] 2-phenyl-5-bromo-1,3-dithiane (III) with thiourea, and was characterized in the picrate form. When (IV) reacted with 2-bromoethane sodium sulfonate or sodium 3-chloropropanesulfonate in an alkaline medium, (V) and (VI) were the respective products. The latter, by heating with mercuric chloride in the presence of  $\text{NaHCO}_3$ , were converted to sodium 2-( $\beta, \beta'$ -mercury dimercaptoisopropylmercapto)ethanesulfonate (VII) and 3-( $\beta, \beta'$ -mercury dimercaptoisopropylmercapto)propanesulfonate (VIII).



\*• In a previous paper [3] we showed the possibility of preparing alkylmercaptoethanesulfonic salts by condensation of S-alkylthiuronic salts with sodium 2-bromoethanesulfonate in alkaline medium.

After mercury was split off from the mercury sodium salt (VII) in alcohol by hydrogen sulfide, the compound was converted to the lead salt 2-( $\beta, \beta'$ -lead dimercaptoisopropylmercapto)ethanesulfonic acid (IX), difficultly soluble in water.



When this salt (IX) was decomposed by hydrogen sulfide in alcohol, an alcoholic solution of 2-( $\beta, \beta'$ -dimercaptoisopropylmercapto)ethanesulfonic acid was formed. It was neutralized with  $\text{NaHCO}_3$ , and the dithiolsulfonate (I) was isolated. The dithiolsulfonate (II) was prepared directly from the mercury sodium salt (VIII) by the splitting off of mercury by hydrogen sulfide in alcohol.

The dithiolsulfonates (I) and (II), and also their  $\alpha$ -isomers described by us previously [3], are of interest for studies on complex-forming substances. The formation of stable complexes with ions of heavy metals is possible, thanks to the presence of sulfide sulfur with its unshared pair of electron in these dithiols.

#### EXPERIMENTAL

2-Phenyl-1,3-dithiane-5-isothiuronium bromide (IV). A solution of 30 g 2-phenyl-5-bromo-1,3-dithiane (III) in 250 ml alcohol was heated with 8.3 g thiourea for four hours, filtered from the suspension, and evaporated on a steam bath. The residue was a viscous, uncrystallizing mass (40 g), soluble in alcohol and water.

Picrate—yellow needles (from 30° alcohol), M.p. 152–153°.

Found %: N 13.62, 13.75.  $\text{C}_{17}\text{H}_{17}\text{O}_7\text{N}_5\text{S}_3$ . Calculated %: N 14.03.

Sodium 2-(2-phenyl-1,3-dithiane-5-mercapto)ethanesulfonate (V). A solution of 30 g (IV), 18 g sodium 2-bromoethane sulfonate and 11 g  $\text{NaOH}$  (1:1:3.3) in 250 ml water was heated for five hours on a steam bath. A precipitate formed on cooling (21.1 g, 69%), which was filtered. Lustrous, colorless flakes, decomposing at 215° (from  $\text{H}_2\text{O}$ ).

Found %: S 33.90; Na 6.25, 6.34;  $\text{H}_2\text{O}$  4.40.  $\text{C}_{12}\text{H}_{15}\text{O}_3\text{S}_4\text{Na} \cdot \text{H}_2\text{O}$ . Calculated %: S 34.04; Na 6.12;  $\text{H}_2\text{O}$  4.78.

S-Benzylthiuronic salt—finely crystalline powder, melting point: 74°.

Found %: N 5.42, 5.80.  $\text{C}_{20}\text{H}_{26}\text{O}_3\text{N}_2\text{S}_5$ . Calculated %: N 5.59.

Sodium 2-( $\beta, \beta'$ -mercury dimercaptoisopropylmercapto)ethanesulfonate (VII). To 10 g sodium 2-phenyl-1,3-dithiane-5-mercaptoethanesulfonate (V) in 125 ml water was added, with heating (bath temperature 60–65°) and stirring, in portions and over a period of 0.5 hour, 7.6 g mercuric chloride and 2.4 g  $\text{NaHCO}_3$  (molar ratio 1:1:1), after which the mixture was heated for another hour at the same temperature. In the solution thus obtained 11.6 g of the mercury sodium salt (VII), which was precipitated by alcohol (125 ml), was determined iodometrically. Yield: 11.4 g (90%). For purposes of analysis, 5 g of the product was dissolved in 20 ml 5%  $\text{NaHCO}_3$  solution and heated for 30 minutes at 60–65°. After filtration from the small amount of suspension, (VII) was precipitated by addition of an equal amount of alcohol. Amorphous powder (3.7 g), decomposition temperature: 202–205°.

Found %: Hg 42.66; Na 5.58. Oxidation equivalent (titration 0.1 N iodine) 239.3.  $\text{C}_5\text{H}_9\text{O}_3\text{S}_4\text{NaHg}$ . Calculated %: Hg 42.73; Na 4.91. Equivalent (M:2) 234.5.

S-Benzylthiuronic salt—amorphous powder, decomposition temperature 175–177°.

Found %: N 4.54, 4.77.  $\text{C}_{13}\text{H}_{20}\text{O}_3\text{N}_2\text{S}_5\text{Hg}$ . Calculated %: N 4.58.

Lead 2-( $\beta, \beta'$ -lead dimercaptoisopropylmercapto)ethanesulfonate (IX). Hydrogen sulfide was passed for 20 minutes through a suspension of 20 g mercury sodium salt (VII) in 100 ml alcohol. The precipitate was isolated and treated with hydrogen sulfide as above in three fresh portions of alcohol (100 ml each). The hydrogen sulfide was removed by passing carbon dioxide through the combined filtrates, and then 10.5 g dimercaptosulfonate salt (I) was determined iodometrically. Its solution was added to a solution of 20 g lead acetate. The yellow precipitate formed was filtered, and washed with boiling water on the filter. This gave 16.2 g (65%) lead salt (IX) as a yellow, amorphous powder.

Found %: Pb 55.90.  $\text{C}_{10}\text{H}_{18}\text{O}_6\text{S}_8\text{Pb}_3$ . Calculated %: Pb 55.89.



Sodium 2-( $\beta,\beta'$ -Dimercaptoisopropylmercapto)ethanesulfonate (I). The finely pulverized salt (IX), in 16 g quantity, was decomposed in alcohol (75 ml) by means of hydrogen sulfide. The filtrate, which was the alcoholic solution of 2-( $\beta,\beta'$ -dimercaptoisopropylmercapto)ethanesulfonic acid (according to iodine titration, 5 g), was partially evaporated, then neutralized with powdered  $\text{NaHCO}_3$  while heated on a steam bath. This, on cooling of the solution, gave 2.4 g (31%) salt (I), as lustrous flakes. It contains one molecule of crystallization water, which is removed on heating in vacuo at 60-65°. Decomposition temperature: 238-241°.

Found %: S 44.12; SH 23.60; Na 8.13;  $\text{H}_2\text{O}$  6.00.  $\text{C}_5\text{H}_{11}\text{O}_3\text{S}_4\text{Na} \cdot \text{H}_2\text{O}$ . Calculated %: S 44.44; SH 22.94; Na 7.98;  $\text{H}_2\text{O}$  6.24.

Sodium 3-(2-phenyl-1,3-dithiane-5-mercapto)propanesulfonate (VI). 35 g of 2-phenyl-1,3-dithiane-5-isothiuronic bromide (IV), 18 g sodium 3-chloropropane sulfonate (obtained from trimethylenedichloro bromide and sodium sulfite [4]) and 12 g NaOH (molar ratio 1:1:3) in 100 ml water was heated for six hours. The solution, on cooling with ice water, gave 53 g precipitated salt (VI) adulterated with NaBr. Recrystallization from water for analysis gave 1.5 g salt (VI) out of 3 g, as colorless crystals decomposing at 193-195°.

Found %: S 33.26, 33.70; Na 6.00, 6.02;  $\text{H}_2\text{O}$  2.10.  $\text{C}_{13}\text{H}_{17}\text{O}_3\text{S}_4\text{Na} \cdot \frac{1}{2}\text{H}_2\text{O}$ . Calculated %: S 33.59; Na 6.03;  $\text{H}_2\text{O}$  2.35.

Sodium 3-( $\beta,\beta'$ -mercury dimercaptoisopropylmercapto)propanesulfonate (VIII). To a solution of 50 g unpurified salt (VI) in 250 ml water was added, in portions under heating on a steam bath (60-65°) for 30 minutes and stirring, 30 g mercuric chloride and 10 g  $\text{NaHCO}_3$ , after which the heating was continued for another hour. To the solution thus obtained was added 300 ml alcohol. Of this product (VIII), 53.6 g was isolated adulterated with NaCl and NaBr, but suitable for the preparation of the dithiolsulfonate (II). From 3 g of the pure salt (VI) in 25 ml water, 2.1 g mercuric chloride and 1.2 g  $\text{NaHCO}_3$  analogously was prepared 3.5 g of sufficiently pure salt (VIII). White, amorphous powder, decomposing at 220°.

Found %: Hg 40.70; Na 4.48. Oxidation equivalent (iodometric titration) 249.2.  $\text{C}_6\text{H}_{11}\text{O}_3\text{S}_4\text{NaHg}$ . Calculated %: Hg 41.49; Na 4.78. Equivalent (M:2) 241.6.

S-Benzylthiuronic salt - amorphous powder decomposing at 138-139°.

Found %: N 4.68, 4.74.  $\text{C}_{14}\text{H}_{22}\text{O}_3\text{N}_2\text{S}_5\text{Hg}$ . Calculated %: N 4.47.

Sodium 3-( $\beta,\beta'$ -dimercaptoisopropylmercapto)propanesulfonate (II). 50 g of finely powdered mercury sodium salt (VIII) was decomposed by hydrogen sulfide in alcohol (twice 500 ml). After separation from mercury sulfide, the filtrate was evaporated in vacuo to ca. 7% concentration of the dimercapto compound. Cooling of the solution to 0° gave 10.9 g product (II) as lustrous flakes; crystallization from alcohol yielded 3.4 g (14%). It contains one molecule of crystallization water, which is removed on heating in vacuo to 60-75°. Decomposition temperature: 219°.

Found %: S 41.66; SH 21.06; Na 7.72;  $\text{H}_2\text{O}$  5.86.  $\text{C}_6\text{H}_{13}\text{O}_3\text{S}_4\text{Na} \cdot \text{H}_2\text{O}$ . Calculated %: S 42.41; SH 21.87; Na 7.61;  $\text{H}_2\text{O}$  5.95.

#### SUMMARY

Sodium 2-(2-phenyl-1,3-dithiane-5-mercapto)propanesulfonate and, correspondingly, sodium 3-(2-phenyl-1,3-dithiane-5-mercapto)propanesulfonate were synthesized by condensation of 2-phenyl-1,3-dithiane-5-isothiuronyl bromide with sodium 2-bromoethanesulfonate and sodium 3-chloropropanesulfonate in an alkaline medium. These compounds were cleaved at the dithiane ring by mercuric chloride in the presence of  $\text{NaHCO}_3$  to give sodium 2-( $\beta,\beta'$ -dimercaptoisopropylmercapto)ethanesulfonate and sodium 3-( $\beta,\beta'$ -dimercaptoisopropylmercapto)propanesulfonate.

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RELATION BETWEEN STRUCTURE AND PROPERTIES OF DYES  
DERIVED FROM BENZANILIDE

III. DISAZO DYES FROM 4,4'-DIAMINO DERIVATIVES OF THE ANILIDE  
OF PHENYLACETIC AND THE BENZYLAMIDE OF BENZOIC ACIDS

B. M. Krasovitskiĭ and V. B. Smelyakova

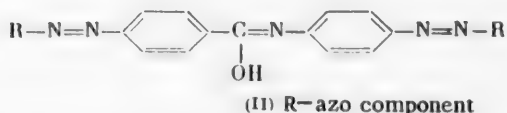
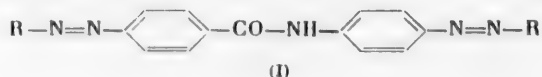
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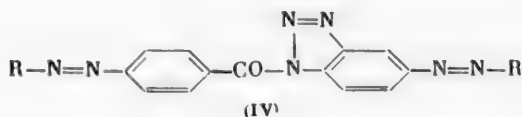
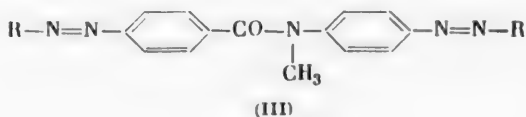
Original article submitted July 12, 1960

Earlier [1, 2] it was assumed that substantivity toward cotton in disazo dyes derived from 4,4'-diaminobenzanilide (I) was connected with possible tautomeric conversion, resulting in the formation of the imidole form (II), containing a much longer chain with conjugated double bonds.



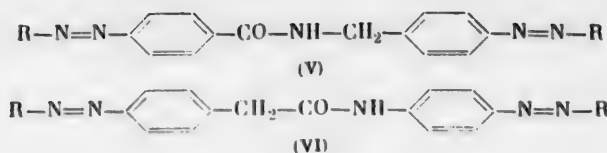
This conversion should be favored by the considerable effect of conjugation in dyes (I), since in their molecules the amide group is linked to two benzene rings, and the latter in their turn are conjugated with the naphthalene rings of the azo components. Thanks to the conjugation effect, the tendency to equalize electron density is enhanced, and this can be achieved on formation of the imidole structure (II).

Taking advantage of this hypothesis, experimental data were brought out which showed that N-methyl derivatives (III) of dyes (I) [2] and dyes (IV) [1] were not direct, since the tautomerism mentioned above was not possible for them.



All disazo dyes derived from benzanilide, isomeric with dyes (I) in which one or both azo groups are in the meta-position to the amide group, are also poorly substantive [3]: The imidole form of those dyes has no such long conjugated double bond chain as form (II). It is also possible that with those the lessened conjugation effect makes it more difficult to tautomerize than does happen with dyes (I).

The properties of dyes (V) and (VI)—the object of the present paper—are further proof of the hypothesis that there exists tautomerism in dyes derived from 4,4'-diaminobenzanilide.



These dyes have a methylene group between the amide group and one of the benzene rings of the diazo component, which methylene group interrupts the conjugated chain in the imidole form, in case the latter has formed. Investigation showed that their affinity for cotton is very different from that of dyes derived from 4,4'-diaminobenzanilide (see table), similar in structure though they may be.

Dye*	$\lambda_{\text{max}}$ , m $\mu$	Affinity, kcal/mole	
		80°	100°
(I)	558 [2]	5.15 [4]	4.22 [4]
(V)	540	0.82	0.70
(VI)	544	1.10	0.84

\* Azo component Ash-acid (coupling in alkaline medium).

Dyes (V) and (VI), as well as dyes (III) studied before [2], are much deeper colored than compounds (I).

In a number of studies devoted to substantivity of direct dyes and azotoles, great significance was attached to the formation of hydrogen bonds between their amide groups and the hydroxyl groups of cellulose (see, for instance, [5, 6]). The slight substantivity of dyes (V) and (VI), also of disazo dyes which are isomeric with dyes (I), indicates that hydrogen bonds which the amide groups could form with cellulose are of only secondary significance for the fixation of dyes on cotton, at least in the case of the dyes under consideration.

#### EXPERIMENTAL\*

##### Intermediate Products

p-Nitrobenzylamide of p-nitrobenzoic acid. A mixture of 10 g p-nitrobenzylamine hydrochloride and 13 g p-nitrobenzoyl chloride was dissolved in 100 ml pyridine. The solution was boiled for 12 hours, cooled, and the reaction product separated by addition of water. The precipitate was filtered, washed with water, and worked up under heating with a dilute soda solution, water, dilute hydrochloric acid, and again with water, to remove adulterating initial product. The nitro compound thus purified was recrystallized from glacial acetic acid. Yield: 4.2 g (26%). Melting point: 214-215°.

Found %: N 14.20, 13.89.  $\text{C}_{14}\text{H}_{11}\text{O}_5\text{N}_3$ . Calculated %: N 13.95.

p-Aminobenzylamide of p-aminobenzoic acid. A solution of 1 g of the dinitro compound in 15 ml phenylhydrazine was boiled on a sand bath for 10 hours. The solution was cooled and a colorless precipitate of the amine formed, which was carefully washed with benzene, and dried. Yield: 0.42 g (52%). Melting point: 197°.

Found %:  $\text{NH}_2$  13.09.  $\text{C}_{14}\text{H}_{15}\text{ON}_3$ . Calculated %:  $\text{NH}_2$  13.28.

p-Nitroanilide of p-nitrophenylacetic acid. The acid chloride of p-nitrophenylacetic acid obtained from 6 g acid\*\* was dissolved in 60 ml benzene, and to the solution was added 5 g p-nitroaniline. The mixture was refluxed for 10 hours, the precipitate filtered and purified of admixed initial product by treatment with a dilute soda solution, water, dilute hydrochloric acid, again water, and recrystallized from glacial acetic acid. Yield: 8 g (60%). M.p. 241°.

Found %: N 13.94, 13.77.  $\text{C}_{14}\text{H}_{11}\text{O}_5\text{N}_3$ . Calculated %: N 13.95.

\* Corrected melting points.

\*\* The acid chloride obtained by the action of p-nitrophenylacetic acid and phosphorus pentachloride [7] was not vacuum distilled, but used directly for further work.

p-Aminoanilide of p-aminophenylacetic acid. Five g p-nitroanilide of p-nitrophenylacetic acid was added in small portions and over a period of one hour to a heated (to boiling) mixture of 70 ml 10% acetic acid and 10 g iron turnings, under vigorous agitation and while continuing the heating. After all of the nitro compound had been added, the reaction mass was heated another hour, while a constant volume was being maintained by additions of boiling 10% acetic acid. After the heating was completed, the precipitate was filtered, and worked up several times with boiling water. All filtrates obtained after separation of the precipitate were combined and neutralized with soda to a weakly alkaline reaction toward litmus paper. For complete precipitation a solution of sodium sulfide was added to the iron aggregate complex (a test for complete precipitation!). The solution was evaporated until crystals of the amine appeared, and then cooled. The p-aminoanilide was filtered and dried. Yield: 1 g (25%), M.p. 166°.

Found %:  $\text{NH}_2$  13.28,  $\text{C}_{14}\text{H}_{15}\text{ON}_3$ . Calculated %:  $\text{NH}_2$  13.28.

#### Preparation and Study of Dyes

The hydrochlorides of p-aminobenzylamide of p-aminobenzoic acid and p-aminoanilide of p-aminophenylacetic acid are very soluble in water, and normally diazotize when a calculated quantity of sodium nitrite is added to their hydrochloric acid solutions. The diazo compounds were caused to react with a small excess of Ash-acid in an alkaline medium, and the pH was maintained high by additions of soda. After 12 hours of standing, the dyes were filtered, purified by the acetate method [8], and finally by chromatography on aluminum oxides. The analysis of the dyes was done by known methods [9].

The affinity of dyes for cotton was determined by the method given in [10], where the magnitude of affinity was calculated on the basis of results obtained on dyeing at a standard dipole 1:100, dye concentration 0.0001 mole, and of sodium chloride 0.02 mole per one liter dye solution. The dyeing was done at 80 and 100° until equilibrium was attained. The effective volume of the cellulose phase was assumed to be 0.3 liter/kg. The dye concentration in solutions was determined colorimetrically on an FÉK-M photoelectrocolorimeter. Control solutions were heated in a thermostat simultaneously with the dye solutions throughout the whole dyeing process.

Absorption maxima of aqueous solutions of the dyes were determined on an SF-2M spectrophotometer.

#### SUMMARY

1. Disazo dyes were synthesized from p-aminobenzylamide of p-aminobenzoic acid and p-aminoanilide of p-aminophenylacetic acid.
2. The introduction of a methylene group between the amide group and one of the benzene rings in dyes from 4,4'-diaminobenzanilide enhances the color and sharply diminishes the affinity for cotton.
3. Hydrogen bonds between amide groups of the dyes studied and the hydroxyl groups of cellulose have no essential significance in the substantivity properties of these dyes.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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# DIRECT DYES DERIVED FROM OXDIAZOLE AND THIODIAZOLE

## III. COMPARATIVE STUDIES OF ISOMERIC DISAZO DYES DERIVED FROM

### 2,5-DIPHENYL-1,3,4-OXDIAZOLE

B. M. Krasovitskii, R. M. Matskevich, and N. I. Mal'tseva

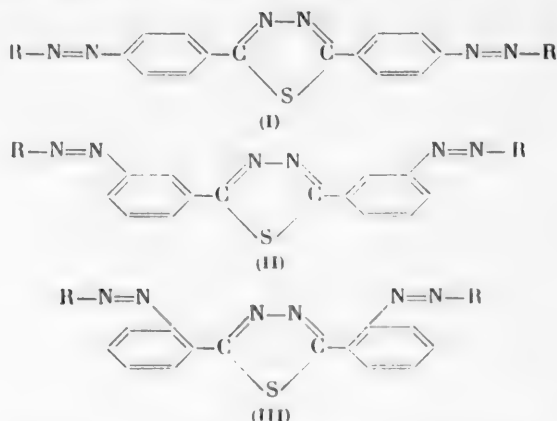
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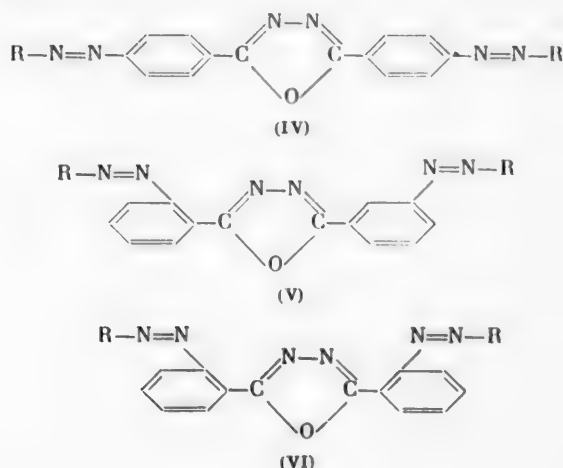
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A study of isomeric disazo dyes (I-III, where R = azo component) containing the thiodiazole nucleus showed [1] that an interruption in the conjugation between chromophoric systems in dyes (II) leads to considerable color deepening and decrease in the affinity for cotton as compared to dyes (I), where the azo groups are para- to internuclear bonds. The small affinity for cotton and deep coloring of dyes (III) (azo groups are ortho- to internuclear bonds made one assume that there is steric hindrance in their molecules.



It was interesting to confirm a regularity noted during studies of dyes (I-III) with analogously constructed diazo dyes (IV-VI) derived from 2,5-diphenyl-1,3,4-oxdiazole. Dyes (IV) were described by us earlier [2]; they turned out to be substantive toward cotton.



The table below gives data on the color of aqueous solutions and the affinity for cotton of dyes (IV-VI); azo components Ash- and Chicago SS-acids, coupled in an alkaline medium.

Dye	Azo component					
	Ash-acid			Chicago SS-acid		
	$\lambda_{\max.}$ (m $\mu$ )	affinity (kcal/mole)		$\lambda_{\max.}$ (m $\mu$ )	affinity (kcal/mole)	
		60°	80°		60°	80°
(IV)	545	4.62	4.35	578	4.74	4.42
(V)	523	2.76	2.60	514	2.76	2.46
(VI)	528	1.95	1.75	528	2.29	1.62

The table demonstrates that in this series as well as with dyes (I-III) the meta-isomers are more deeply colored and have considerably less affinity for cotton than do the para-isomers; this relationship also prevails when para- and ortho-isomers are compared.

Thus, the regularities assumed earlier during studies of dyes containing the thiodiazole ring are validated in the case of their oxdiazole analogs.

#### EXPERIMENTAL

2,5-Bis(2-nitrophenyl)-1,3,4-oxdiazole. A mixture of 15 g N,N'-bis(2-nitrobenzoyl)-hydrazine and 22.5 g phosphorus pentachloride was heated on an oil bath at 140-150° until the flask contents turned liquid. The liquid was cooled with finely crushed ice. An oily substance then formed, which was treated several times with a 2% solution of caustic soda, and then with water. After some time, the oil crystallized, the residue was filtered off, and the substance was dried and recrystallized from butanol with activated charcoal. Melting point: 195°, which agreed with literature data [3]. Yield: 3 g (21%).

2,5-Bis(3-nitrophenyl)-1,3,4-oxdiazole was described as a by-product of the reaction between N,N'-bis(3-nitrobenzoyl)hydrazine and phosphorus pentachloride [4]. We synthesized it in the following manner. Seven g N,N'-bis(3-nitrobenzoyl)hydrazine was dissolved under reflux in 20 ml nitrobenzene, 15 ml thionyl chloride added to the solution, and boiled for one hour. The following day the precipitate which formed was filtered, washed with benzene, and treated with a 2% caustic soda solution and with water. Melting point: 226°, agreeing with literature data [4]. Yield: 3.6 g (55%).

2,5-Bis(2-aminophenyl)-1,3,4-oxdiazole was obtained like the formerly-described para-isomer [2] by the reduction of the corresponding nitro compound with sodium disulfide in a water-pyridine solution: 4.5 g of 2,5-bis(2-nitrophenyl)-1,3,4-oxdiazole was refluxed in 45 ml pyridine and then treated over a period of one hour in boiling solution and dropwise with 270 ml sodium disulfide solution prepared by dissolving 32 g sulfur and 240 g crystalline sodium sulfide (Na<sub>2</sub>S · 9H<sub>2</sub>O) in a mixture of 625 ml water and 100 ml pyridine. The solution was boiled for another hour, cooled, and poured into one liter water. The precipitate which formed was filtered, washed several times with water, dried, and recrystallized from benzene.\* Melting point: 226-227°. Yield: 1 g (28%).

Found %: NH<sub>2</sub> 12.59, 12.62. C<sub>14</sub>H<sub>12</sub>ON<sub>4</sub>. Calculated %: NH<sub>2</sub> 12.70.

2,5-Bis(3-aminophenyl)-1,3,4-oxdiazole was synthesized in two ways.

a) Analogously to the product described above, by reduction of 2,5-bis(3-nitrophenyl)-1,3,4-oxdiazole with sodium disulfide in water-pyridine solution. The resulting product was purified via the hydrochloride. Yield from 1 g nitro compound: 0.53 g (65%), m.p. 247°.

Found %: NH<sub>2</sub> 12.36, 12.36. C<sub>14</sub>H<sub>12</sub>ON<sub>4</sub>. Calculated %: NH<sub>2</sub> 12.70.

b) By reduction of the same nitro compound with sodium hydrosulfite: 2.5 g of 2,5-bis(3-nitrophenyl)-1,3,4-oxdiazole and 25 ml alcohol was heated to boiling with a reflux condenser on a steam bath, 50 ml water added to it, and under boiling small portions of 20 g hydrosulfite were added over a period of one hour. With sufficient addition of the latter, the precipitate gradually dissolved. After all of the hydrosulfite had been added, the mixture

\*The reduction product contains impurities insoluble in benzene, which we did not pursue.



was heated for another hour, the solution evaporated to one third its volume, cooled to room temperature, and the reduction product converted by addition of concentrated hydrochloric acid to a precipitate which sometimes precipitates in the form of a fast-hardening gum, and obviously is the sulfamine derivative. The precipitate was separated from the solution and boiled with an excess of 5% hydrochloric acid; the amine hydrochloride formed on hydrolysis of the sulfamine derivative dissolved. The former was filtered into an excess of ammonia; a flaky precipitate of amine formed, which was dried and then melted at 246-247°. Yield: 1 g (50%).

In order to prove that the amines described above are derivatives of 2,5-diphenyl-1,3,4-oxdiazole, we deaminated them. We dissolved 0.1 g diamine in a mixture of 20 ml water, 1 ml concentrated hydrochloric acid, cooled the solution to 0°, and added a calculated quantity of sodium nitrite. The filtered solution of the diazo compound was then thoroughly mixed and treated with 1 g potassium hypophosphite, placed on ice for three hours, and allowed to stand overnight at room temperature. The precipitate which formed was filtered, washed with water, dried, and recrystallized from 50% alcohol. Deamination of both amines gave products which melted at 135-136°; the literature gives m.p.: 135-136° [5], 138° [6].

Dyes from 2,5-bis(2-aminophenyl)- and 2,5-bis(3-aminophenyl)- derivatives of 1,3,4-oxdiazole. The amines were diazotized by addition of a calculated quantity of sodium nitrite to their hydrochloric acid solutions and cooled to 5°. Coupling with Ash- and Chicago SS-acids was done in an alkaline medium, the high pH of which was maintained by additions of the required amount of soda. Since the very water-soluble dyes from 2,5-bis(2-aminophenyl)-1,3,4-oxdiazole could not be precipitated by addition of sodium chloride, we precipitated them with hydrochloric acid; the resulting precipitate was filtered, dissolved in a minimum of water, and to the solution we added, under slight heating, soda in an amount necessary to convert the dyes to sodium salts. The solutions obtained were purified chromatographically on aluminum oxides and evaporated to dryness on a water bath.

Dyes from 2,5-bis(3-aminophenyl)-1,3,4-oxdiazole were rid of mineral impurities by means of the acetate method [7], and then their water solutions were treated chromatographically on aluminum oxides. Analyses of all dyes were done by known methods [8].

The affinity of the dyes for cotton was determined by the data given in [9], where the magnitude of affinity was calculated on the basis of results obtained on dyeing at 1:100 vat coefficient, dye concentration 0.0001 mole and sodium chloride 0.02 mole per one liter dye solution. The effective volume of the cellulose phase was assumed to be 0.3 liter/kg. The dyeing was done at 60 to 80° until equilibrium was attained. The dye concentration in the solutions was determined colorimetrically on an FÉK-M photoelectrocolorimeter. During the whole dyeing process control solutions were heated in a thermostat simultaneously with the dye solutions.

Maximum absorption of aqueous dye solutions was determined on an SF-2M spectrophotometer.

#### SUMMARY

1. Disazo dyes were synthesized from 2,5-bis(3-aminophenyl)- and 2,5-bis(2-aminophenyl) derivatives of 1,3,4-oxdiazole; affinity for cotton and color of aqueous solutions of the dyes obtained were studied.
2. Disazo dyes derived from 2,5-diphenyl-1,3,4-oxdiazole in which the azo group is ortho- or meta- to the bonds between nuclei are more deeply colored than their para-isomers, and the latter lose considerable affinity for cotton.
3. The regularities and relation between structure, cotton affinity and color previously assumed during studies of dyes containing the thiodiazole ring are confirmed here in the case of their oxdiazole analogs.

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# STUDIES OF AROMATIC ALKYLATED AMINES

## III. N,N-DIMETHYL-2-M-XYLIDINE

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In the first communication it was shown [1] that tetramethyl- and tetraethyl-o-phenylenediamines are sterically hindered due to the steric proximity of the tertiary amino groups. This is manifested by the impossibility of azo coupling and nitrosation, and also by the considerably higher basicity constants of tetramethyl- and tetraethyl-o-phenylenediamines than those of ordinary aromatic amines. A graphic confirmation of the steric hindrance are the Stewart models of these diamines.

Continuing the studies on steric hindrance of tertiary amines, we turned to N,N-dimethyl-2-m-xylylidine (I). According to literature data, it is incapable of reacting with diazo compounds, aldehydes and nitrous acid [2], i.e., with substances with which N,N-dimethylaniline reacts readily. This is explained by the presence of two methyl groups in the ortho-positions to the dimethylamino group, which hinder the coplanar arrangement of the molecule [3].

Determination of basicity constants, however, showed that the methylation of 2-m-xylylidine increases the basicity only by one degree of magnitude (see table), while the methylation of o-phenylenediamine increases the basicity constant by two, and ethylation by three, degrees of magnitude.

The Stewart model of N,N-dimethyl-2-m-xylylidine (I) (Figure 1) shows that although the dimethylamino- and methyl groups are very tightly spaced, they can still be coplanar with the benzene ring. In this arrangement the dimethylamino group should activate the para-carbon atom of the ring. For this reason, we thought it interesting to reinvestigate the tendency of dimethylxylylidine to react with p-nitrodiazobenzene and nitrous acid.

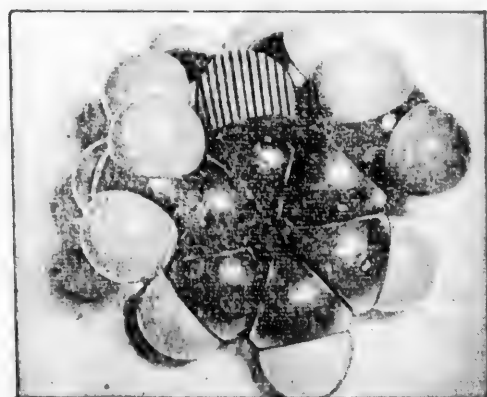
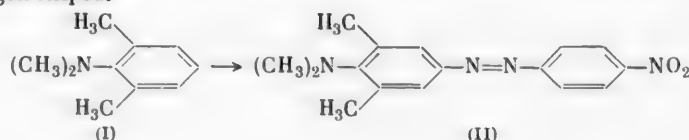


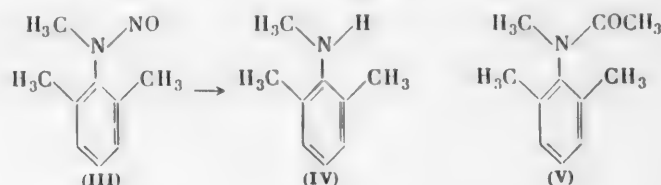
Fig. 1. Stewart model of N,N-dimethyl-2-m-xylylidine. The atoms of carbon are black, of hydrogen light, of nitrogen striped.



The reaction with p-nitrodiazobenzene was conducted in an acetic acid medium in the presence of sodium acetate. A red color appeared on addition of the diazo solution to a solution of dimethylxylylidine (I), and after 15 to 20 hours a red precipitate formed. The dye (II) is very soluble in nearly all organic solvents. In suspension it dyes wool to a yellow-orange color. For purification purposes the dye is dissolved in benzene and precipitated with petroleum ether. The yellow alcohol solution of the dye turned a cherry color on addition of one to two drops of a 20% NaOH solution; on acidification it turned yellow again. The product did not change on heating with concentrated hydrochloric acid for 5-10 minutes: The indicator properties shown above remained. However, heating of the product in alcohol or benzene partially resinsified it. Yield of dye (II): 30%. The unreacted portion of dimethylxylylidine (I) can be isolated reversibly from the reaction solution. Thus, the experiment showed that azo coupling takes place, although with a small yield of dye (II).

The reaction with nitrous acid was conducted in the manner described earlier [1]. The nitrosation product is not soluble in hydrochloric acid and is obtained as an oil extractable with ether. Yield: 21.4%. The unreacted dimethylxylidine, about 60%, is extracted with ether after the solution has been made alkaline with sodium bicarbonate.

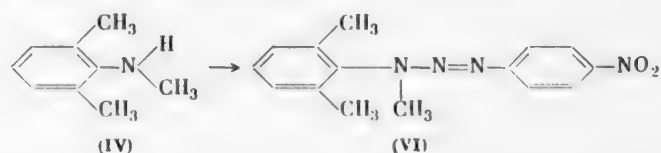
With an excess of sodium nitrite (2 and 5.5 gram-mole per one gram-mole dimethylxylidine) as used for nitrosation, the same product formed, and its yield was greater (44.3% and 85%, respectively). The insolubility of the nitrosation product in hydrochloric acid indicates that it is not the C-nitroso derivative. Elementary analysis shows that the composition corresponds to that of the N-nitroso-N-methyl-2-m-xylidine (III).



To prove the structure, the product obtained (III) was hydrolyzed by hydrochloric acid, which gave a substance with a camphor odor characteristic of monomethylxylidine (IV). The latter was identified in the form of the acetyl derivative (V) from its melting point with a known sample of N-methyl-N-acetyl-2-m-xylidine synthesized by the Friedländer method [3].

A case of nitrosation of a tertiary amino group with substitution of  $\text{CH}_3$  by NO has been described in the literature [4-7]. It is also known that the addition rate of the nitroso group to nitrogen is several times higher than that to carbon [8]. This is of decisive significance in the case of N,N-dimethyl-2-m-xylidine, in which the para-carbon atom is slightly activated.

The orange diazoamino compound (VI) is formed by reaction of monomethyl-2-m-xylidine with p-nitrodiazobenzene in an acetic acid medium and in the presence of sodium acetate.



The orange alcoholic solution of this diazoamino compound (VI) quickly turns cherry red on heating in the presence of dimethylaniline and hydrochloric acid. After cooling, a cherry red precipitate is obtained from the solution, which is 4-dimethylamino-4'-nitroazobenzene (VIII). The latter, according to melting point and absorption spectrum, is identical with the known 4-dimethylamino-4'-nitroazobenzene (VIII) (Figure 2).

According to the absorption spectrum, the diazo compound (VI) differs from the azo dye (II) by a shift in the maximum of absorption by 15  $m\mu$  toward the short waves [ $\lambda_{\text{max}}$  for compound (VI) is 360  $m\mu$ ], and also by a considerably higher extinction value.

All these data prove that when monomethyl-2-m-xylidine and dimethyl-2-m-xylidine react with p-nitrodiazobenzene, the residue of p-nitrodiazobenzene enters the amino group in the former case, and in the latter, para to the amino group.

A comparison of results obtained with the given data in the first paper shows that unhindered tertiary aromatic amines (for instance, dimethylaniline, tetramethyl-m-phenylenediamine, et al.) form azo dyes in good yield, nitrosate in the para position, and according to basicity constants hardly differ from the corresponding primary amines.

Sterically hindered, noncoplanar tertiary aromatic amines (for instance, tetramethyl-o-phenylenediamine) do not undergo azo coupling and nitrosation. Their basicity constants are considerably higher than those of corresponding unhindered primary amines.

In this regard, N,N-dimethyl-2-m-xylidine occupies an intermediate position: Upon reaction with an active diazo compound, it forms azo dyes in low yields, nitrosates at the amino group, and according to the basicity constant differs from 2-m-xylidine only by one degree of magnitude.

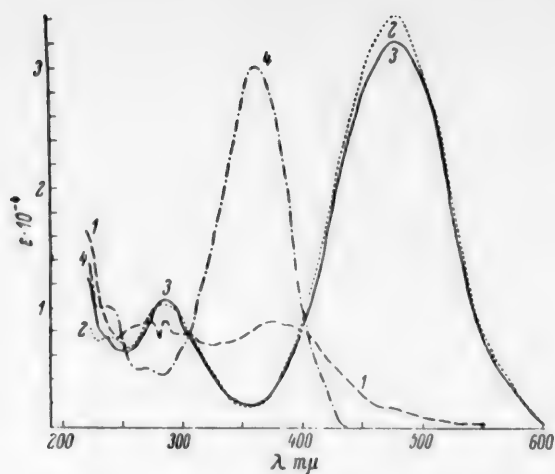


Fig. 2. Absorption spectra of alcoholic solutions. 1) Azo dye (II); 2) azo dye (VIII); 3) product of reaction between diazoamino compound (VI) and dimethylaniline; 4) diazoamino compound (VI).

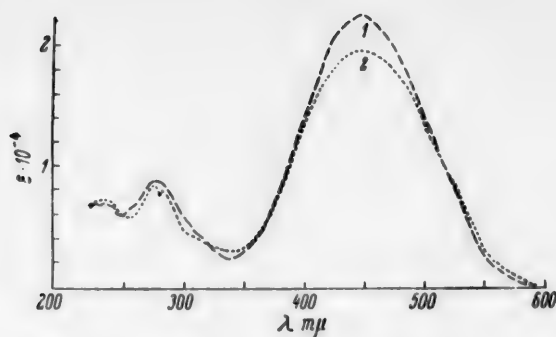


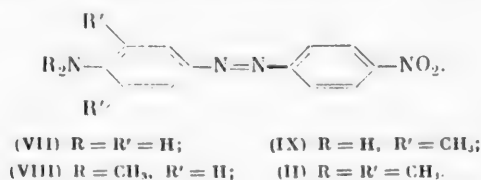
Fig. 3. Absorption spectra of alcoholic solutions of azo dyes. 1) Compound (VII); 2) compound (IX).

Here, however, one should notice that the magnitude of the basicity constant is no measure of the coplanarity disturbance of a sterically hindered amine, since the introduction of one methyl group in the ortho position on the one hand hinders coplanarity of the amino group (increased basicity), but on the other hand it slightly increases the cation stability of the given amine by blocking the positively charged nitrogen (lowering of basicity). The introduction of a second methyl group at the ortho position only slightly changes the noncoplanarity of the molecule, but considerably enhances the blocking of the nitrogen, lowering the basicity [9] (see table).

We thought it possible to gain some knowledge of the degree of noncoplanarity of the dimethylamino group in dimethyl-2-m-xylylidine by studying the ultraviolet absorption spectrum of the azo dye prepared by us.

It could be expected that in *p*-aminoazo dyes with an unhindered amino group the maximum of the absorption band in the ultraviolet is shifted toward the longer waves according to the increase of basicity. In a more basic amino group the unshared pair of electrons has more mobility, and thus takes part in the coupling to a greater degree. It is known [10-12] that an increased degree of coupling leads to a shift in the absorption band maximum toward longer waves. To the extent of increased noncoplanarity of the molecule, the coupling of an amino group with a benzene ring is disturbed, and in that case the maximum of the absorption band should be displaced toward the short waves.

We studied four *para*-aminoazo dyes obtained by us by azo coupling of *p*-nitrodiazobenzene with aniline (VII), dimethylaniline (VIII), 2-m-xylylidine (IX), dimethyl-2-m-xylylidine (II).



The ultraviolet spectra of all compounds were taken in alcoholic solution on an SF-4 spectrophotometer (Figs. 2 and 3 and table).

The given data prove that in reality an increase in basicity of the initial amine in dyes with unhindered amino groups leads to a shift in the maximum of absorption toward longer waves, and to enhanced absorption intensity.

In the case of the dimethylxylylidine azo dye (II), the steric hindrance leads to a shift in the absorption maximum toward short waves by 103 mμ, as compared to dye (IX), and in the case of the dimethyl-*o*-toluidine azo dye (X), described in the literature in [15, 16], the maximum shifts in the same direction by 43 mμ.

It is interesting to note that with 2,3-dimethyl-4-dimethylamino-4'-nitroazobenzene, isomeric with azo dye (II), the absorption maximum also shifts toward short waves ( $\lambda_{\text{max}}$  425 mμ [17]), but somewhat less than in the case

No. of compound	Initial amine		Azo dye (coupling with p-nitrodiazo-benzene)			
	name	pK <sub>b</sub> at 25°		empirical formula	λ <sub>max</sub> (mμ)	ε
		in water [13]	in 50% alcohol [14]			
(IX)	2-m-Xylidine . . . . .	—	10.58	C <sub>14</sub> H <sub>14</sub> O <sub>2</sub> N <sub>4</sub>	440	19450
(VII)	Aniline . . . . .	9.42	9.75	C <sub>12</sub> H <sub>10</sub> O <sub>2</sub> N <sub>4</sub>	450*	22600
(VIII)	N,N-Dimethylaniline . . . . .	8.94	9.74	C <sub>14</sub> H <sub>14</sub> O <sub>2</sub> N <sub>4</sub>	478* •	34200
(X)	N,N-Dimethyl-o-toluidine . . . . .	—	8.93	C <sub>15</sub> H <sub>16</sub> O <sub>2</sub> N <sub>4</sub>	435 [15, 16]	—
(II)	N,N-Dimethyl-2-m-xylidine	—	9.31	C <sub>16</sub> H <sub>18</sub> O <sub>2</sub> N <sub>4</sub>	375	8760

\* According to data in [18], λ<sub>max</sub> 445 mμ.

•• According to data in [17], λ<sub>max</sub> 478 mμ; according to [18], λ<sub>max</sub> 480 mμ.

of azo dye (II). This is explained by the fact that here the dimethylamino group of the dye, just as in the dimethyl-o-toluidine azo dye (X), is blocked by only one methyl group in the ortho position.

#### EXPERIMENTAL

N,N-Dimethyl-2-m-xylidine (I). A mixture of 18.65 g 2-m-xylidine, 145 ml methanol, 70 ml water, 18.8 g CaCO<sub>3</sub> and 90 g methyl iodide was heated on a steam bath for 12-15 hours. The excess CaCO<sub>3</sub> was filtered off (5.37 g). The filtrate was diluted with water and extracted with ether. The ether extract was dried with potash and the ether distilled off. To the substance thus obtained was added 22 ml acetic anhydride and the mixture boiled for four hours. It was poured into 200 ml warm water. It was allowed to stand overnight. The solution was made alkaline with soda (34.3 g), extracted with ether, the ether solution treated with dilute hydrochloric acid. The hydrochloric acid solution was alkalinized with a 20% NaOH solution. The base formed was extracted with ether. The ether extract was dried with potash, the ether distilled, and the residue redistilled in vacuo. Melting point: 87° at 23 mm, n<sub>D</sub><sup>15</sup> 1.5150. Yield: 20.42 g (95.8%).

Azocoupling—N,N-dimethyl-2-m-xylidine with p-nitrodiazobenzene. Dimethyl-2-m-xylidine (8.94 g) was dissolved in 220 ml glacial acetic acid, 88 ml water added, and 33.7 g crystalline sodium acetate. The solution thus obtained was cooled with ice and poured together with the diazo solution prepared as follows: 8.28 g p-nitroaniline was dissolved under heating in hydrochloric acid (22 ml conc. HCl and 15 ml water). The clear solution thus obtained was cooled rapidly and to it was added gradually, under stirring and cooling, a solution of 4.15 g NaNO<sub>2</sub> in 22 ml water. Light yellow solution.

The reaction mixture was allowed to stand at room temperature. The red dye which formed was filtered the following day, washed with water, and dried. This gave 5.3 g (30%) of a substance. The precipitate was dissolved in acetic acid and precipitated with water, filtered, and dried. It was dissolved in benzene and reprecipitated with petroleum ether. The melting point of the 4-dimethylamino-3,5-dimethyl-4'-nitroazobenzene thus purified was 155-157° (decomposition).

Found%: N 17.80, 17.57. C<sub>16</sub>H<sub>18</sub>O<sub>2</sub>N<sub>4</sub>. Calculated %: N 18.78.

The azo dye is very difficult to burn. The given analytical values had to be obtained on combustion in the presence of vanadium oxide. Without vanadium oxide the results would be 4-5% lower.

Unreacted dimethylxylidine was recovered in small quantities on neutralization of the acetic acid solution with sodium carbonate, after filtration of the dye.

Nitrosation of N,N-dimethyl-2-m-xylidine. a) To 9 g dimethyl-2-m-xylidine was added 13 ml conc. HCl and 60 g ice. This was cooled with ice under constant stirring, and to it gradually added a solution of 5 g sodium nitrite in 34 ml water. No precipitate. An oily layer formed, which was allowed to stand for four hours. The mixture was extracted with ether, dried with magnesium sulfate, the ether evaporated, and the remaining N-nitroso-N-methyl-2-m-xylidine (III) vacuum distilled. The product was a yellow oil. B.p.: 113-115° at 5.5 mm, n<sub>D</sub><sup>18</sup> 1.5405. Yield: 2.12 g (21.4% per used dimethylxylidine or 63% per reacted).

Found %: N 16.97, 17.18. C<sub>9</sub>H<sub>12</sub>ON<sub>2</sub>. Calculated %: N 17.06.



The hydrochloric acid solution was alkalinized with sodium carbonate (5.6 g), extracted with ether, the ether solution dried with potash. The ether was evaporated and the residue vacuum distilled. B.p. 91.5° at 26 mm,  $n_D^{19}$  1.5140; weight: 5.4 g (60%)—initial dimethylxylidine.

b) Dimethylxylidine (8.4 g) was nitrosated in mixture with 20 g ice, 30 ml water and 22 ml conc. HCl by a solution of 8 g sodium nitrite in 40 ml water under constant stirring and cooling. After the sodium nitrite had been added, the reaction mixture was at once extracted with ether, the ether solution twice washed with a solution of sodium bicarbonate. Further treatment as shown above. This gave 4.1 g N-nitroso-N-methyl-2-m-xylidine (44.3% per used or 68.6% per reacted dimethylxylidine), b.p.: 112-114° at 5.5 mm,  $n_D^{19}$  1.5402 and 3.0 g (35.7%) initial dimethylxylidine, b.p.: 76° at 20 mm,  $n_D^{15.5}$  1.5146.

c) Dimethylxylidine (8.2 g), 55 g ice, 75 ml water and 60 ml conc. HCl. Gradually a solution of 21 g sodium nitrite in 95 ml water was added. The mixture was allowed to stand overnight. Further treatment as above. This gave 7.65 g nitrosomethylxylidine (85% per used dimethylxylidine). B.p.: 119.5-120° at 6.5 mm,  $n_D^{20}$  1.5396. Initial dimethylxylidine was not detected.

Hydrolysis of N-nitroso-N-methyl-2-m-xylidine. Nitrosomethylxylidine (4.1 g) and 40 ml of 25% hydrochloric acid was refluxed for 2.5 hours. After cooling crystals appeared, which were extracted with ether. The hydrochloric acid solution was alkalinized with a 20% NaOH solution and extracted with ether. The ether extract was dried with potash. The ether was evaporated and the residue vacuum distilled. B.p.: 99° at 22 mm,  $n_D^{15.5}$  1.5400. Yield: 1.35 g (40%) N-methyl-2-m-xylidine (IV)—a mobile liquid with a characteristic camphor odor.

Substance (IV) (0.4 g) was boiled with 2 ml acetic anhydride for two hours. The solution was poured into 10 ml cold water and allowed to stand overnight. Then it was neutralized with sodium carbonate (2.2 g) and extracted with ether. The ether solution was treated with dilute hydrochloric acid, the ether evaporated, and the crystals of N-methyl-N-acetyl-2-m-xylidine (V) obtained recrystallized from boiling water. M.p.: 91-92° ([2]). A mixed melting point test with a known prepared sample of N-methyl-N-acetyl-2-m-xylidine gave no m.p. depression.

Reaction of N-methyl-2-m-xylidine with p-nitrodiazobenzene. The reaction was conducted as with dimethyl-2-m-xylidine. Substance (IV) (0.55 g) was dissolved in 15 ml glacial acetic acid, 6 ml water, and 2.3 g crystalline sodium acetate added to it. The solution was cooled and to it was added the diazo solution prepared from 0.55 g p-nitroaniline. The solution turned orange, and a precipitate of the diazoamino compound formed quickly, which was filtered after 30 minutes and washed several times with water. It was recrystallized from aqueous alcohol (20 ml alcohol and 5 ml water). M.p.: 109-110°. Yield of diazoamino compound (VI): 0.95 g (82.5%).

Found %: C 63.33; H 5.58; N 19.64.  $C_{15}H_{16}O_2N_4$ . Calculated %: C 63.36; H 5.67; N 19.71.

Reaction of N-(p-nitrophenylazo)-N-methylamino-2,6-dimethylbenzene (VI) with dimethylaniline. Diazoamino compound (VI) (0.5 g) was dissolved in 50 ml alcohol, to it added 0.22 g dimethylaniline and 0.5 ml conc. hydrochloric acid. All was heated on a steam bath for 1.5 hours. On cooling to room temperature a cherry red precipitate formed, i.e., the azo dye (VIII), which was filtered, washed with alcohol, and dried in a desiccator. This gave 0.1 g (20%). M.p.: 232-234° [19]. A mixed melting point test with a known sample of 4-dimethylamino-4-nitroazobenzene gave no melting point depression.

Preparation of p-aminoazo dyes. 4-Dimethylamino-4'-nitroazobenzene (VIII) melting at 232-233.5° (from toluene) [19] and 4-amino-3,5-dimethyl-4'-nitroazobenzene (IX) melting at 175-177° (from dilute alcohol) [2] were prepared by the method described above.

4-Amino-4'-nitroazobenzene (VII) was prepared by azo coupling of p-nitroazobenzene with aniline- $\omega$ -methyl-sulfonic acid, followed by hydrolysis of the dye obtained. M.p.: 209-212° [20].

For spectroscopic studies, all azo dyes were purified chromatographically in acetone solution on aluminum oxides, and eluted with benzene.

#### SUMMARY

1. When N,N-dimethyl-2-m-xylidine reacted with p-nitrodiazobenzene, an azo dye was formed in 30% yield.
2. Nitrosation of N,N-dimethyl-2-m-xylidine gave an N-nitroso derivative.
3. Reaction of N-methyl-2-m-xylidine with p-nitrodiazobenzene gave a diazoamino compound. Its ultra-violet absorption spectrum was measured.



4. The Stewart model shows that the dimethylamino group in the molecule of N,N-dimethyl-2-m-xylylidine can be coplanar with the benzene ring, but this position is hindered. This explains the chemical properties of N,N-dimethyl-2-m-xylylidine described above.

5. Ultraviolet spectra of azo dyes prepared by azo coupling of p-nitrodiazobenzene with aniline, dimethylaniline, 2-m-xylylidine and N,N-dimethyl-2-m-xylylidine were measured.

6. It was shown that with sterically hindered azo dyes the maximum of absorption bands shifts toward the short waves and the absorption intensity is considerably lowered.

7. Ultraviolet absorption spectra of their azo dyes can serve as a measure of noncoplanarity in tertiary aromatic amines.

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# STUDIES OF AROMATIC ALKYLATED AMINES

## IV. SIGNIFICANCE OF THE STERIC FACTOR IN THE QUATERNIZATION OF DIMETHYL- AND DIETHYLANILINES

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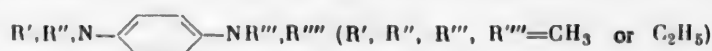
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In a previous communication [1] it was shown that when tetraalkyl-p-phenylenediamines



reacted with methyl iodide and ethyl iodide, the result was quaternization of that nitrogen atom which is least shielded by alkyls. It is known that ethylated anilines are stronger bases than methylated ones. Consequently, in the reactions shown, the steric factor dominates the basicity factor.

In the present work we investigated the role of the steric factor in analogous reactions of alkyl halides (methyl iodide, ethyl iodide and benzyl iodide) with dimethylaniline and diethylaniline.

Since the determination of velocity constants of these reactions presented no problem, we conducted the reaction of alkyl halides with an equimolar mixture of dimethyl- and diethylaniline. In this manner, similar to the previous work [1], the dimethylamino- and diethylamino group was subjected to the effect of an alkyl halide under identical conditions and simultaneously.

In the case of derivatives of p-phenylenediamine, however, the reactivity of a second amino group dropped after quaternization of one of the amino groups, and thus, despite an excess of alkyl halide, no reaction occurred with the second molecule of the latter. In the given case it was necessary to use strictly equimolar quantities of both amines and alkyl halide. The reacting substances were boiled in acetone solution for five hours, and then the mixture of components was separated. The quaternary ammonium salt obtained was weighed and identified.

Insofar as the quaternary ammonium iodide salts dissolved differently in acetone, each tertiary amine individually was caused to react under identical conditions with alkyl halides, while the yield of the quaternary salt formed was determined (Table 1).

TABLE 1. Reaction of Dimethyl- and Diethylaniline with Alkyl Iodides

Tertiary amine	RI	Yield, %	
		$\text{C}_6\text{H}_5\text{N}(\text{CH}_3)_2 \cdot \text{RI}$	$\text{C}_6\text{H}_5\text{N}(\text{C}_2\text{H}_5)_2 \cdot \text{RI}$
Dimethylaniline. . . . .	$\text{CH}_3\text{I}$	74.7	—
Diethylaniline. . . . .	$\text{CH}_3\text{I}$	—	22.0-24.8
Mixture of dimethyl- and diethylanilines. .	$\text{CH}_3\text{I}$	73.3-74.0	—
Dimethylaniline. . . . .	$\text{C}_6\text{H}_5\text{CH}_2\text{I}$	96.0	—
Diethylaniline. . . . .	$\text{C}_6\text{H}_5\text{CH}_2\text{I}$	—	5.4
Mixture of dimethyl- and diethylanilines. .	$\text{C}_6\text{H}_5\text{CH}_2\text{I}$	81.8-90.0	—

TABLE 2. Reaction between Methyl-diethyl- and Dimethylethylphenylammonium Iodide with Dimethylaniline

Initial quaternary salt	Medium	Yield of trimethylphenylammonium iodide (in %)
Methyldiethylphenylammonium iodide	Toluene and dimethylaniline	8.98
	Chlorobenzene and dimethylaniline	3.85
	Dimethylaniline*	82.70
Dimethylethylphenylammonium iodide	Toluene and dimethylaniline	—
	Chlorobenzene and dimethylaniline	8.98
	Dimethylaniline*	93.70

\* A tenfold molar excess was used.

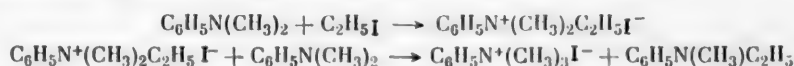
In all alkylation experiments of a mixture of dimethyl- and diethylanilines only addition products of alkyl halide to dimethylaniline were isolated. This shows that under the conditions it is practically only the dimethylaniline which reacts with the alkyl halides. The products were identified by melting points with known synthesized quaternary compounds, and by solubility, which differs greatly for derivatives of dimethyl- and diethylaniline.

The data in Table 1 also indicate that, individually, dimethylaniline and diethylaniline react with methyl iodide with different ease. With benzyl iodide, which by size of the radical quite surpasses methyl iodide, dimethylaniline reacts with comparative ease (in mixture as well as individually), while diethylaniline taken individually reacts more difficultly with benzyl iodide. Attempts to prepare diethylphenylbenzylammonium iodide in another manner (by reaction of an equimolar mixture of reagents over a period of two days [2]) gave no positive results.

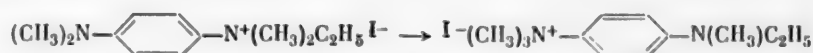
It is known that the benzylating agent—dimethylphenylbenzylammonium chloride (leucotrope)—is easily prepared by mixing equimolar quantities of dimethylaniline and benzyl chloride at room temperature, whereupon the reaction product is formed in two hours in nearly quantitative yield [3, 4]. Our experiments showed that under analogous conditions diethylaniline and benzyl chloride give no appreciable quantity of a quaternary salt, not even after 80 days. Boiling of the reagents in benzene [5] gave no positive results either, not even after prolonged interaction (10 hours).

Investigation of Stewart models demonstrated graphically that addition of the benzyl radical to the diethylaniline nitrogen is greatly hindered sterically.

Experiments with ethyl iodide proved that the latter is less reactive in the given reactions than is benzyl iodide. In order to get a good yield of dimethylethylphenylammonium iodide (90-94%), it is necessary to boil the reaction mixture in acetone solution for 48 hours. The synthesis of triethylphenylammonium iodide is described in the literature [6]. According to that record, we succeeded in preparing only crystals (12.1%) which were difficult to purify. Under the conditions of our experiments (boiling for five hours in acetone solution), the mixture of dimethylaniline, diethylaniline, and ethyl iodide yielded only 14.4% dimethylethylphenylammonium iodide. When the heating time was extended to 40 hours, the yield increased to 44-54%, but at the same time some (7-10%) trimethylphenylammonium iodide also was formed. The following reaction may explain its formation:

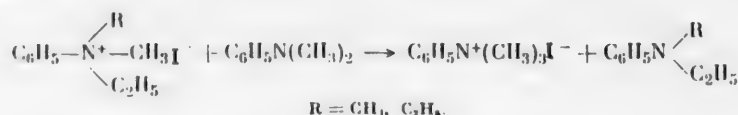


The second reaction is "intermolecular transmethylation," analogous to "intramolecular transmethylation" described by us earlier [1].



We thought it necessary to prove more exactly the possibility of side reactions and to follow the role of the steric factor, also temperature conditions in these reactions.

For this purpose we heated a mixture of dimethylaniline and dimethylethylphenylammonium iodide and methyldiethylphenylammonium iodide, respectively, for one hour in solvents with different boiling points. Table 2 gives these experimental data.



The given data show that with high reaction temperatures and large excess of dimethylaniline the latter displaces diethylaniline and methylethylaniline from their methyl iodides, forming trimethylphenylammonium iodide in high yield. The reaction is not reversible. Consequently, in these reactions of "intermolecular transmethylation" the steric factor is the determining one.

## EXPERIMENTAL

### Reaction of a Mixture of Dimethyl- and Diethylaniline with Alkyl Iodides

a) With methyl iodide and benzyl iodide. To 0.025 gram-mole dimethylaniline and 0.025 gram-mole diethylaniline dissolved in 40 ml anhydrous acetone was added rapidly under stirring and boiling, 0.025 gram-mole alkyl iodide in 16 ml anhydrous acetone. A precipitate of the alkyl iodide of dimethylaniline formed sometimes at once, sometimes gradually. The boiling and stirring was continued for five hours. The following day the precipitate was filtered, washed with anhydrous acetone and absolute ether. The acetone washings were combined with the main filtrate.

Trimethylphenylammonium iodide was prepared in analytically pure form from methyl iodide; it melted at 228-229° [7] and the yield was 4.60-4.69 g (73.3-74.0%); from benzyl iodide—dimethylbenzylphenylammonium iodide, m.p. 152-154°; after crystallization from benzene, m.p. 164-165° [8], weight 6.94-7.63 g (81.8-90.0%).

The solvent was evaporated from the acetone filtrate. The remaining oil and small quantity of crystals were steam distilled. Aniline oils which had not reacted were distilled off.\* After ether extraction, drying and ether evaporation, the weight of the residue was 3.3-3.22 g (iodomethylation, 48-49%••), 2.8-3.19 g (iodobenzylation, 42-47%••).

A small quantity of the alkyl iodide of dimethylaniline could be isolated from the aqueous solution after the removal of aniline oils.

b) With ethyl iodide. Under the conditions described above, heating for 40 hours in a flask, the product was an insignificant amount of precipitate which after crystallization from the least volume of anhydrous alcohol yielded 0.45-0.65 g (7-10%) colorless, shiny leaflets of trimethylphenylammonium iodide, m.p.: 228-229°. The main reaction product, namely, dimethylethylphenylammonium iodide, is soluble in acetone and was recovered from an aqueous solution obtained after steam distillation of the aniline oils. The latter were obtained in 3.72-3.45 g (55.2-51.2%) yields. The remaining thick, yellow oil, 3.05-3.75 g (44.1-54.2%) was purified by crystallization from anhydrous alcohol, or reprecipitation from the latter with absolute ether. Colorless, crystalline residue, m.p.: 135.5-136.5° [9].

The alkyl iodides with which the prepared compounds were compared were synthesized under analogous conditions in the absence of the second amine. The product yields are shown above.

Reactions of diethylaniline. a) With benzyl chloride. According to Rodionov [3], in the cold no reaction occurred on many hours of boiling and heating to 175-180°. Repetition of data given in [5] also gave no positive results, although the boiling time was extended to 10 hours.

b) With benzyl iodide. We boiled 0.0125 gram-mole diethylaniline with 30% excess benzyl iodide in 10 ml anhydrous acetone for five hours. Addition of ether gave a viscous oil, which was treated 6-7 times with ether. The residue (2.5 g, m.p. 86-88°) was dissolved in 15 ml anhydrous alcohol, boiled with charcoal, and to the filtrate was added 180 ml ether, which gave 0.25 g (5.44%) oil, which quickly crystallized. After repeated reprecipitation, m.p.: 94-96°•••

\*In the case of iodobenzylation, benzyl iodide is also distilled off.

••In percent of weight of initially used aniline mixture.

•••The authors in [2] give m.p. 111° for benzyldiethylphenylammonium iodide.

Found %: N 3.63, 3.61; I 34.50, 34.59.  $C_{17}H_{22}NI$ . Calculated %: N 3.81; I 34.56.

**Intermolecular transmethylation.** The quaternary compound, 0.03 gram-mole (methyldiethylphenylammonium iodide, m.p. 102° [10], or dimethylethylphenylammonium iodide, m.p. 135.5-136.5° [9]), and a tenfold excess of dimethylaniline were boiled together for one hour. When a high temperature had been reached, crystals appeared on the walls of the flask. After completion of the reaction the mixture was filtered and several times washed with anhydrous acetone.

When the reaction was carried out in a chlorobenzene or toluene medium, we used an equimolar mixture of the quaternary compound and dimethylaniline and a tenfold (by weight) quantity of solvent.

In all experiments one and the same product was the result, with m.p. 228-229°, i.e. trimethylphenylammonium iodide. Only when dimethylethylphenylammonium iodide reacted with dimethylaniline in a toluene medium the initial compounds with m.p. 135.5-136.6° was recovered. Yields of individual experiments are given in Table 2.

#### SUMMARY

1. When alkyl halides react with dimethylaniline or diethylaniline in equimolar mixture, practically only dimethylaniline takes part in the reaction, i.e., an amine in which the tertiary amino group is less sterically hindered.
2. The steric factor plays an analogous role in reactions of intermolecular transmethylation. Thus, when dimethylethylphenylammonium iodide is heated with dimethylaniline, trimethylphenylammonium iodide and methylethylaniline are formed.

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**N<sup>1</sup>-DIAROXYPHOSPHINYL-N<sup>2</sup>-(N<sup>3</sup>-ARYLTHIOCARBAMINYL)-  
-ARENAMIDINES [N<sup>1</sup>-ARYL-N<sup>2</sup>-(N<sup>3</sup>-DIAROXYPHOSPHINYLMINO-  
OAROYL)-THIOUREAS]**

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Many thiourea derivatives exhibit well-defined physiological activity [1]. Various arylthioureas, one of the nitrogen atoms of which is bonded with an esterified phosphoric acid group, are insecticides, fungicides and chemotherapeutic media [2]. Thus, synthesis of new types of phosphorus-containing thiourea derivatives is of interest.

Acid chlorides of N-diaroxyphosphinyliminocarboxylic acids [3] react with potassium thiocyanate (cf. [4]), forming isothiocyanates of N-diaroxyphosphinyliminocarboxylic acids



The reaction proceeds readily on mixing an acetone solution of potassium thiocyanate with solutions of acid chlorides in methylene chloride or acetone at 0-5°.

Isothiocyanates of N-diaroxyphosphinyliminocarboxylic acids are viscous yellow liquids, quite soluble in ether, methylene chloride, acetone, benzene, with difficulty in carbon tetrachloride and petroleum ether.

In almost every case, on reacting acid chlorides of N-diaroxyphosphinyliminocarboxylic acids with potassium thiocyanate, as well as isothiocyanates, small amounts of high-melting polymeric compounds are formed. On reacting the acid chloride of N-diphenoxyphosphinylimino-p-nitrobenzoic acid with potassium thiocyanate under very varied conditions, only a yellow, high-melting polymer is formed (m.p. 300-350°), insoluble in water and the usual organic solvents. On prolonged boiling of the polymer with alcohol a small amount is formed of the diphenyl ester of p-nitrobenzoylamidophosphoric acid. The outward appearance of the polymer is unchanged on boiling with aqueous acid or alkali solutions.

Isothiocyanates of N-diaroxyphosphinyliminocarboxylic acids polymerize on distillation in vacuo, and thus the crude products were treated with aromatic amines without purification. This resulted in 60-80% yields of N<sup>1</sup>-diaroxyphosphinyl-N<sup>2</sup>-(N<sup>3</sup>-arylthiocarbaminy)-arenamidines [N<sup>1</sup>-aryl-N<sup>2</sup>-(N<sup>3</sup>-diaroxyphosphinyliminoaroyl)-thioureas](I), which were comparatively low-melting, crystalline substances, insoluble in water, possessing the properties of very weak acids (Table 1).



They readily dissolve in aqueous-alcoholic caustic alkali solutions and on acidifying the alkaline solutions they are obtained in unchanged form. In alcoholic solutions they titrate with caustic alkalis in presence of phenolphthalein as monobasic acids, but do not dissolve in aqueous alkali solutions.

On heating aqueous-alcoholic solutions of compounds (I) with acids they are hydrolyzed to diesters of acylamidophosphoric acids,



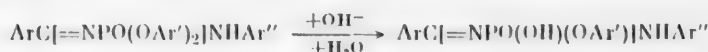


On alkaline hydrolysis in aqueous-alcoholic solutions the amidine grouping is unchanged, but saponification of one aroxyl group bound to the phosphorus takes place with formation of  $N^1$ -monoaroxyphosphorylphosphinyl- $N^1$ -( $N^3$ -arylthiocarbaminy)-arenamidines (II), which are high-melting, crystalline substances, insoluble in water, possessing the properties of weak acids (Table 2).



They dissolve readily in 0.5-1.0 N solutions of sodium bicarbonate and carbonate and in weak caustic soda solutions. On reacting with concentrated caustic alkali solutions, compounds (II) are salted out from solution as oily salt layers. Compounds (II) are readily soluble in aqueous-alcoholic caustic alkali solutions. On acidifying the alkaline solutions they are obtained unchanged. In alcoholic solutions they titrate with phenolphthalein as monobasic acids.

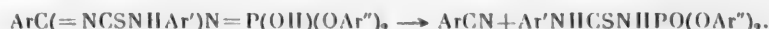
The groupings  $\text{=NPO}(\text{OR})_2$  and  $\text{=NPO}(\text{NHR})_2$  in diesters and diamides of the  $N$ -acylamidophosphoric acids  $\text{AcNHPO}(\text{OR})_2$  and  $\text{AcHNPO}(\text{NHR})_2$  are saponified with great difficulty on boiling in alkaline solutions [5]. This is explained by the fact that in such solutions the ions  $[\text{AcNPO}(\text{OR})_2]^-$  or  $[\text{AcNPO}(\text{NHR})_2]^-$  occur, and are stable toward alkaline hydrolysis. Although the grouping  $\text{=NPO}(\text{OR})_2$  also occurs in compounds (I), the molecule is a neutral complete monoamidodiester of phosphoric acid, not forming salts in aqueous solutions of alkalis; consequently, saponification in an alkaline medium proceeds readily, with formation of an ion of an acid monoamidomonoester stable toward hydrolysis, in the same manner as saponification of complete esters of polybasic acids proceeds, e.g., sulfuric acid [6], triaroxy- and trialkoxyphosphazacyls [7], phosphoric acid [6], etc., to the corresponding acid esters. If this reasoning is correct, every compound of similar structure, e.g.,  $N$ -diphenoxyphosphinyl- $N^1$ -arylbenzamidines and  $N^1$ -diphenoxyphosphinylbenzamide [8], should also be readily saponified by alkalis with formation of acid monoamidomonoesters stable in alkaline solutions. Experimentation has confirmed the correctness of the proposition. On boiling  $N$ -diphenoxyphosphinyl- $N^1$ -arylbenzamidines and  $N$ -diphenoxyphosphinylbenzamide in aqueous-alcoholic alkaline solutions, they are saponified to  $N$ -monophenoxymonohydroxyphosphinyl- $N^1$ -arylbenzamidines (correspondingly to  $N$ -monophenoxymonohydroxyphosphinylbenzamide):



In their chemical nature, compounds (I) are simultaneously derivatives of  $N$ -arylthiourea and of  $N$ -phosphorylated amidines. Thus, on their thermal cleavage it would be expected that they, like thiourea (cf. [9]), would decompose to arylisothiocyanates and  $N$ -diaroxyphosphinylarenamidines:



or like amidine derivatives phosphorylated at the nitrogen (cf. [8]) would be split into nitriles and  $N$ -diaroxyphosphinyl- $N^1$ -arylthioureas:



On heating compounds (I) with somewhat higher melting points in a vacuum of 0.5-1.0 mm, they are split only in the first manner, with formation of arylisothiocyanates and  $N$ -diaroxyphosphinylarenamidines (Table 3). This is evidently explained by splitting in the second manner proceeding at considerably higher temperatures and therefore being practically negligible.

#### EXPERIMENTAL

**Isithiocyanates of  $N$ -Diaroxyphosphinyliminocarboxylic Acids.** To a solution, cooled to  $0^\circ$ , of 0.01 g-mole of the acid chloride of  $N$ -diaroxyphosphinyliminocarboxylic acid in 20 ml of anhydrous acetone or methylene chloride was added with constant stirring a solution of 0.01 g-mole of dry potassium thiocyanate in 20 ml of anhydrous acetone, cooled to  $0^\circ$ . Potassium chloride then precipitated, and the solution developed a bright yellow color. The mixture was stirred for 10 minutes and left to stand at room temperature for 10-20 hours. The potassium chloride precipitate and the small quantity of yellow polymer were filtered off and the solution concentrated in vacuo at room temperature. In the residue were found isothiocyanates of  $N$ -diaroxyphosphinyliminocarboxylic acids as thick, bright yellow, transparent liquids. Yields almost quantitative.

**Reaction of Potassium Thiocyanate with the Acid Chloride of  $N$ -Diphenoxyphosphinylimino- $p$ -nitrobenzoic Acid.** To a solution of 0.01 g-mole of the acid chloride of  $N$ -diphenoxyphosphinylimino- $p$ -nitrobenzoic acid in 40 ml

TABLE 1. N<sup>1</sup>-Diaroxyposphinyl-N<sup>2</sup>-(N<sup>3</sup>-arylthiocarbaminy)-arenamidines

Ar	Ar'	Ar''	Yield, %	M. p.	Crystal characteristics, medium from which crystallized
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	75	145–146 <sup>o</sup>	Colorless needles, alcohol
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	74	138–139	Colorless needles, alcohol
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	65	130–132	Colorless needles, alcohol
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<i>o</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	67	127–128	Colorless needles, alcohol
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	73	125–126	Colorless needles, alcohol
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	67	127–128	Colorless needles, alcohol
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	68	130–131	Colorless needles, alcohol
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	74	131–132	Colorless needles, alcohol
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<i>o</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	61	142–143	Colorless needles, alcohol
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	69	128–129	Colorless needles, alcohol
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	78	139–140	Colorless cohering needles, alcohol
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<i>α</i> -C <sub>10</sub> H <sub>7</sub>	69	123–124	Colorless needles, alcohol
C <sub>6</sub> H <sub>5</sub>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	50	134–135	Colorless needles, alcohol
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	81	153–154	Colorless cohering needles, alcohol
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	71	144–145	Colorless needles, alcohol
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	73	151–152	Colorless needles, alcohol
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	64	158–159	Colorless needles, alcohol
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	67	154–155	Colorless needles, alcohol
<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	60	147–148	Bright yellow cohering needles, alcohol
<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	84	156–157	Bright yellow needles, alcohol
<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	80	157–158	Bright yellow needles, alcohol
3,5-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	66	165–166	Colorless cohering needles, alcohol
3,5-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	63	156–157	Bright yellow needles, alcohol + dioxan
3,5-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	65	150–151	Bright yellow needles, alcohol + dioxan
3,5-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	61	156–157	Colorless needles, alcohol

\* Calculated as equivalent 1.00 for all compounds.

\*\* All compounds are insoluble in water, petroleum ether and ether at boiling point. †) ing point; =) insoluble at boiling point.

$\text{ArC[=NPO(OAr')}_2\text{]NHCSNHAr''}$ 

Found, %	Empirical formula	Calculated*, %	Solubility**				
			alco- hol	ben- zene	$\text{CCl}_4$	ace- tone	dioxan
N 8.44, 8.57. Equiv. 0.98, 1.02 N 8.17, 8.35	$\text{C}_{20}\text{H}_{22}\text{O}_3\text{N}_3\text{SP}$ $\text{C}_{27}\text{H}_{24}\text{O}_3\text{N}_3\text{SP}$	N 8.62 N 8.38	+	+	-	+	+
N 8.29, 8.19. Equiv. 0.99, 1.01 N 8.06, 8.26	$\text{C}_{27}\text{H}_{24}\text{O}_3\text{N}_3\text{SP}$ $\text{C}_{27}\text{H}_{24}\text{O}_4\text{N}_3\text{SP}$	N 8.38 N 8.12	+	+	-	+	+
N 8.09, 8.16	$\text{C}_{27}\text{H}_{24}\text{O}_4\text{N}_3\text{SP}$	N 8.12	+	+	-	+	+
N 7.86, 8.01	$\text{C}_{26}\text{H}_{21}\text{O}_3\text{N}_3\text{SPCl}$	N 8.05	+	+	-	+	+
N 7.71, 7.77	$\text{C}_{26}\text{H}_{20}\text{O}_3\text{N}_3\text{SPCl}_2$	N 7.55	+	+	-	+	+
N 7.14, 7.17	$\text{C}_{26}\text{H}_{21}\text{O}_3\text{N}_3\text{SPBr}$	N 7.42	+	+	-	+	+
N 10.20, 10.20 N 10.34, 10.36 N 10.51, 10.56	$\text{C}_{26}\text{H}_{21}\text{O}_5\text{N}_4\text{SP}$ $\text{C}_{26}\text{H}_{21}\text{O}_5\text{N}_4\text{SP}$ $\text{C}_{26}\text{H}_{21}\text{O}_5\text{N}_4\text{SP}$	N 10.52 N 10.52 N 10.52	-	-	=	+	+
N 7.61, 7.67	$\text{C}_{30}\text{H}_{24}\text{O}_3\text{N}_3\text{SP}$	N 7.82	+	+	-	+	+
N 7.30, 7.41; S 5.61, 5.70	$\text{C}_{26}\text{H}_{20}\text{O}_3\text{N}_3\text{SPCl}_2$	N 7.55; S 5.76	+	+	-	+	+
N 8.05, 8.20; Cl 6.70, 6.76	$\text{C}_{26}\text{H}_{21}\text{O}_3\text{N}_3\text{SPCl}$	N 8.05; Cl 6.79	+	+	-	+	+
N 7.90, 7.91; Cl 6.46, 6.53	$\text{C}_{27}\text{H}_{23}\text{O}_3\text{N}_3\text{SPCl}$	N 7.84; Cl 6.62	+	+	-	+	+
N 10.06, 10.07 N 7.14, 7.18	$\text{C}_{26}\text{H}_{20}\text{O}_5\text{N}_4\text{SPCl}$ $\text{C}_{26}\text{H}_{19}\text{O}_3\text{N}_3\text{SPCl}_3$	N 9.88 N 7.11	-	-	=	+	+
N 7.16, 7.19. Equiv. 0.99, 1.01 N 10.29, 10.47	$\text{C}_{27}\text{H}_{21}\text{O}_3\text{N}_3\text{SPCl}_3$ $\text{C}_{26}\text{H}_{21}\text{O}_5\text{N}_4\text{SP}$	N 6.95 N 10.52	+	+	-	+	+
N 10.05, 10.08	$\text{C}_{27}\text{H}_{23}\text{O}_5\text{N}_4\text{SP}$	N 10.25	-	-	=	+	+
N 12.35, 12.47	$\text{C}_{26}\text{H}_{20}\text{O}_7\text{N}_5\text{SP}$	N 12.13	-	-	=	+	+
N 12.16, 12.32	$\text{C}_{26}\text{H}_{20}\text{O}_7\text{N}_5\text{SP}$	N 12.13	-	-	=	+	+
N 11.89, 12.10	$\text{C}_{27}\text{H}_{22}\text{O}_7\text{N}_5\text{SP}$	N 11.84	-	-	=	+	+
N 13.42, 13.62	$\text{C}_{26}\text{H}_{19}\text{O}_9\text{N}_6\text{SP}$	N 13.50	-	-	=	+	+
N 10.49, 10.51	$\text{C}_{26}\text{H}_{18}\text{O}_7\text{N}_5\text{SPCl}_2$	N 10.83	-	-	=	+	+

Readily soluble at 20°; +) readily soluble at boiling point; -) soluble with difficulty at boil-

TABLE 2.  $N^1$ -Monoaroxymonohydroxyphosphinyl- $N^2$ -( $N^3$ -arylthiocarbaminy)-arenamidines

Ar	Ar'	Ar''	Yield, %	M. p.	Crystal characteristics, medium from which crystallized
$C_6H_5$	$C_6H_5$	$C_6H_5$	85	227—228°	Colorless prisms, alcohol + dioxan
$C_6H_5$	$C_6H_5$	p- $CH_3C_6H_4$	87	217—218	Colorless prisms, alcohol + dioxan
$C_6H_5$	$C_6H_5$	p- $ClC_6H_4$	83	219—220	Colorless prisms, alcohol + dioxan
$C_6H_5$	$C_6H_5$	p- $NO_2C_6H_4$	83	234—235	Bright yellow prisms, alcohol + dioxan
p- $ClC_6H_4$	p- $ClC_6H_4$	$C_6H_5$	92	251—252	Bright yellow needles, acetone
p- $ClC_6H_4$	p- $ClC_6H_4$	p- $CH_3C_6H_4$	84	244—245	Bright yellow needles, dioxan
3,5-( $NO_2$ ) $_2C_6H_3$	$C_6H_5$	$C_6H_5$	91	275—276 (decomp)	Bright yellow microcrystalline powder**
3,5-( $NO_2$ ) $_2C_6H_3$	p- $ClC_6H_4$	$C_6H_5$	85	267—268 (decomp.)	Bright yellow microcrystalline powder**

\* See Table 1; all compounds are insoluble in water, petroleum ether, ether and  $CCl_4$  at

\*\* For method of purification, see EXPERIMENTAL.

of methylene chloride, acetone, or acetonitrile with cooling to 0° and constant stirring was gradually added a solution of 0.01 g-mole of potassium thiocyanate in 40 ml of acetone. After standing for 15–25 hours the reaction mixture was converted into a compact, solid, yellow-colored mass. The product was drawn off, washed with water, alcohol, ether, and dried. Yield 70%, m.p. 300–350°. The substance was insoluble in the usual organic solvents. On boiling with a ten-fold amount of methanol for 2 hours the outward appearance of the product was unchanged, but from the mother liquor after filtration about 1% of the diphenyl ester of p-nitrobenzoylamidophosphoric acid could be obtained.

$N^1$ -Diaroxyphosphinyl- $N^2$ -( $N^3$ -arylthiocarbaminy)-arenamidines (I) (Table 1). To a filtered solution of the crude isothiocyanate of N-diaroxyphosphinyliminocarboxylic acid, obtained from 0.01 g-mole of the acid chloride of N-diaroxyphosphinyliminocarboxylic acid, in 30–100 ml of anhydrous ether was added a solution of 0.01 g-mole of a mine in 10–20 ml of anhydrous ether, and the mixture left to stand for 5–10 hours at 20°. The resulting precipitate, or the oil which crystallized on rubbing with a glass rod, was drawn off, washed with ether, dried and recrystallized.

#### Hydrolysis of $N^1$ -Diaroxyphosphinyl- $N^2$ -( $N^3$ -arylthiocarbaminy)-arenamidines.

A. In Aqueous-Alcoholic Hydrochloric Acid Solution. A mixture of 0.002 g-mole of compound (I), 20–40 ml of alcohol and 0.20 ml of concentrated hydrochloric acid was boiled under reflux condenser for 3.5 hours. The precipitate gradually dissolved. The transparent solution was concentrated in vacuo. The remaining oil was washed with water and to the oily residue was added a small amount of alcohol. The diesters of the acylamidophosphoric acids crystallized rapidly. They were drawn off, washed with alcohol and recrystallized. Yields 50–60%. Identified by means of mixed melting point samples.

B. In Aqueous-Alcoholic Caustic Soda Solution. A mixture of 0.002 g-mole of compound (I), 15–20 ml of alcohol, and 1 ml of 2.0 N aqueous caustic soda solution was boiled under reflux condenser for 2 hours. The bright yellow or bright brown (in the case of 3,5-dinitrobenzamide derivatives) solution was acidified with dilute hydrochloric acid until an acid reaction was given with congo. The  $N^1$ -monoaroxymonohydroxyphosphinyl- $N^2$ -( $N^3$ -arylthiocarbaminy)-arenamidines (II) (Table 2) settling out into the precipitate were drawn off, washed with water, dried and recrystallized. The 3,5-dinitrobenzamide derivatives could not be recrystallized, and so were purified by reprecipitation by acid from alkaline aqueous-alcoholic solutions. From the mother liquor were obtained the corresponding phenols in 50–70% yield.

Hydrolysis of N-Diphenoxyphosphinyl- $N^1$ -arylbenzamidines. A mixture of 0.002 g-mole of N-diaroxyphosphinyl- $N^1$ -arylbenzamide, 1 ml of 2.0 N caustic soda solution and 40 ml of alcohol was boiled for 15 hours. The pre-



Found, %	Empirical formula	Calculated, %	Solubility**			
			alco- hol	ben- zene	ace- tone	dioxan
N 10.21, 10.24; Equiv. 0.99, 1.01	$\text{C}_{20}\text{H}_{18}\text{O}_3\text{N}_3\text{PS}$	N 10.21; Equiv. 1.00	—	—	+	+
N 9.82, 9.95; P 7.04, 7.24; Equiv. 1.01, 1.02	$\text{C}_{21}\text{H}_{20}\text{O}_3\text{N}_3\text{PS}$	N 9.88; P 7.28; Equiv. 1.00	—	—	+	+
N 9.34, 9.44; Cl 7.92, 8.06	$\text{C}_{20}\text{H}_{17}\text{O}_3\text{N}_3\text{SPCl}$	N 9.43; Cl 7.95	—	—	+	+
N 12.26, 12.37	$\text{C}_{20}\text{H}_{17}\text{O}_5\text{N}_4\text{SP}$	N 12.28	—	—	+	+
Cl 14.94, 14.96; N 8.89, 8.98	$\text{C}_{20}\text{H}_{16}\text{O}_3\text{N}_3\text{SPCl}_2$	Cl 14.76; N 8.75	—	—	+	+
N 8.53, 8.55; Equiv. 1.01, 1.04	$\text{C}_{21}\text{H}_{18}\text{O}_3\text{N}_3\text{SPCl}_2$	N 8.50; Equiv. 1.00	—	—	+	+
N 13.88, 14.09	$\text{C}_{20}\text{H}_{16}\text{O}_7\text{N}_5\text{SP}$	N 13.97	—	—	—	—
N 13.22, 13.42; Cl 6.46, 6.70	$\text{C}_{20}\text{H}_{15}\text{O}_7\text{N}_5\text{SPCl}$	N 13.07; Cl 6.62	—	—	—	—

the boiling point.

precipitate went into solution. The solution was filtered and acidified until acid to congo. The product obtained was drawn off, washed with water and crystallized. The substances were very sparingly soluble in alcohol and dioxan, practically insoluble in water, petroleum ether, ether, benzene, carbon tetrachloride and acetone.

N-Monophenoxy-monohydroxyphosphinyl-N<sup>1</sup>-phenylbenzamidine. Yield 50%, prisms (from alcohol), m.p. 182–184°.

Found %: N 7.95, 8.00; P 8.61, 8.77. Equ. 1.01.  $\text{C}_{19}\text{H}_{17}\text{O}_3\text{N}_2\text{P}$ . Calculated %: N 7.95; P 8.79. Equ. 1.00.

N-Monophenoxy-monohydroxyphosphinyl-N<sup>1</sup>-p-chlorophenylbenzamidine. Yield 65%, prisms (from an alcohol-dioxan mixture), m.p. 191–193°.

Found %: Cl 9.12, 9.29.  $\text{C}_{19}\text{H}_{16}\text{O}_3\text{N}_2\text{PCl}$ . Calculated %: Cl 9.17.

TABLE 3. Thermal Cleavage of N<sup>1</sup>-Diaroxyphosphinyl-N<sup>2</sup>-(N<sup>3</sup>-arylthiocarbaminyl)-arenamidines:  $\text{ArC}(\text{=NPO}(\text{OAr}')_2)\text{NHCSNHAr}'' \rightarrow \text{ArC}(\text{=NPO}(\text{OAr}')_2)\text{NH}_2 + \text{Ar}''\text{NCS}$

Ar	Ar'	Ar''	Cleavage temperature	N-diaroxy- pharylare- namidine yield, %	Arylthio- cyanate yield, %
$\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5$	145–155°	80	68
$\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5$	<i>o</i> -Br $\text{C}_6\text{H}_4$	155–166	89	74
<i>m</i> -NO <sub>2</sub> $\text{C}_6\text{H}_4$	$\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5$	160–170	83	77
<i>p</i> -Cl $\text{C}_6\text{H}_4$	$\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5$	155–165	76	81
<i>p</i> -Cl $\text{C}_6\text{H}_4$	<i>p</i> -Cl $\text{C}_6\text{H}_4$	$\text{C}_6\text{H}_5$	160–170	85	74

Hydrolysis of N-Diphenoxyphosphinylbenzamidine. To a solution of 0.01 g-mole of N-diphenoxyphosphinylbenzamidine in 25 ml of alcohol was added 10 ml of 2.0 N caustic soda, and the mixture boiled for 5–6 hours. The alcohol was distilled off in vacuo. To the residue, a mixture of an oil and a crystalline substance, was added 5–6 ml of

water and the mixture acidified with concentrated hydrochloric acid until acid to congo. The resulting crystals of N-monophenoxymonohydroxyphosphinylbenzamidines were drawn off, washed with water and dried. Yield 43%, colorless prisms (from alcohol), m.p. 216-217°. The product was sparingly soluble in all organic solvents.

Found %: N 10.62, 10.68; P 11.30. Equ. 0.99.  $C_{13}H_{15}O_3N_2P$ . Calculated %: N 10.14; P 11.23. Equ. 1.00.

Thermal Cleavage of  $N^1$ -Diaroxyphosphinyl- $N^2$ -( $N^3$ -arylthiocarbaminy)-arenamidines (Table 3). Compound (I) (0.01 g-mole) was heated on an oil bath in a Claisen flask fitted with thermometer and capillary in a vacuum of 0.5-1.0 mm. Decomposition proceeded at bath temperature 145-170° (see Table 3) over a period of 5-10 minutes. The arylisothiocyanates were then distilled off and identified by boiling point, refractive index and conversion to the symmetric diarylthiourea. In the flask remained a glassy mass, which crystallized after addition of a few drops of alcohol and rubbing with a glass rod. The crystals of N-diaroxyphosphinylarenamidines were drawn off, washed with a small amount of alcohol and recrystallized. Identified by means of a mixed melting point sample.

#### SUMMARY

1. By the action of potassium thiocyanate on acid chlorides of N-diaroxyphosphinyliminocarboxylic acids, isothiocyanates of N-diaroxyphosphinyliminocarboxylic acids were prepared.
2. By the action of amines on isothiocyanates of N-diaroxyphosphinyliminocarboxylic acids,  $N^1$ -diaroxyphosphinyl- $N^2$ -( $N^3$ -arylthiocarbaminy)-arenamidines were prepared.
3. By alkaline hydrolysis of  $N^1$ -diaroxyphosphinyl- $N^2$ -( $N^3$ -arylthiocarbaminy)-arenamidines,  $N^1$ -monooxy-monohydroxyphosphinylimino- $N^2$ -( $N^3$ -arylthiocarbaminy)-arenamidines were prepared.
4. By acid hydrolysis of  $N^1$ -diaroxyphosphinyl- $N^2$ -( $N^3$ -arylthiocarbaminy)-arenamidines, diesters of acylamidophosphoric acids were obtained.
5. By saponification, in an alkaline medium, of N-diphenoxyphosphinyl- $N^1$ -arylbenzamidines and N-diphenoxyphosphinylbenzamidines, N-monophenoxymonohydroxyphosphinyl- $N^1$ -arylbenzamidines and N-monophenoxymonohydroxyphosphinylbenzamidines, respectively, were obtained.
6. By thermal cleavage of  $N^1$ -diaroxyphosphinyl- $N^2$ -( $N^3$ -arylthiocarbaminy)-arenamidines, N-diaroxyphosphinylarenamidines and arylisothiocyanates were obtained.

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# AMINO ALCOHOLS OF THE ACETYLENE SERIES

## II. 1,1-DISUBSTITUTED 5-DIALKYLAMINOPENTYNOLS WITH VARIOUS TRIPLE BOND POSITIONS\*

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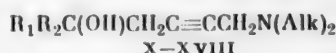
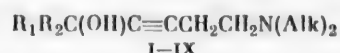
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In the opinion of a series of investigators, the presence in the molecule of the dialkylaminoalkyl esters of substituted glycolic acids  $R_1R_2C(OH)COOCH_2CH_2N(Alk)_2$  of a short chain of five atoms between the hydroxyl and the nitrogen atom is the structure most favorable for manifestation of cholinolytic activity [2]. Moreover, it has been established that in unsaturated analogs of acetylcholine the influence of the acetylene group on the activity of the compound is similar to the influence of the carboxyl group [3]. If such a rule were also observed among acetylcholine antagonists, amino alcohols (I-IX) would appear, from this point of view, similar to the dialkylaminoalkyl esters of substituted glycolic acids, and high cholinolytic activity would be expected of them. The cholinolytic properties of the aminopentynols isomeric to them (X-XVIII) would be displayed more weakly.



The present work deals with synthesis of compounds (I-XVIII). Among similar substances, only 1,1-diphenyl-5-dimethylaminopentyne-3-ol-1 (X) is described in the literature [4].

Attempts to prepare substituted 5-dialkylaminopentyne-2-ols [compounds (I-IX)] by alkylation with dialkylaminoethyl chlorides of tertiary ethynylcarbinols in the form of their sodium, lithium, bromomagnesium and silver derivatives in liquid ammonia, toluene, ether, or ethanol did not lead to the desired results. In some cases nonvolatile products of basic character were obtained in low yield, their identification, however, being unsuccessful.

We were successful in achieving synthesis of amino alcohols by reacting sodium derivatives of dialkylaminobutynes with ketones according to the scheme



The reaction was carried out in a mixture of liquid ammonia and ether and was completed by boiling in ether. A total of nine substituted 5-dialkylaminopentyn-2-ols were synthesized: 1,1-diphenyl-5-dimethylaminopentyn-2-ol-1 (I), 1,1-diphenyl-5-diethylaminopentyn-2-ol-1 (II), 1,1-diphenyl-5-piperidinopentyn-2-ol-1 (III), 1-phenyl-1-cyclohexyl-5-dimethylaminopentyn-2-ol-1 (IV), 1-phenyl-1-cyclohexyl-5-dimethylaminopentyn-2-ol-1 (V), 1-phenyl-1-cyclohexyl-5-piperidinopentyn-2-ol-1 (VI), 1-dimethylamino-4-(9'-hydroxyfluorenyl-9')butyne-3 (VII), 1-diethylamino-4-(9'-hydroxyfluorenyl-9')butyne-3 (VIII), 1-piperidino-4-(9'-hydroxyfluorenyl-9')butyne-3 (IX), and also their hydrochlorides (Tables 1 and 3).

To prepare the dialkylaminobutynes used in this synthesis the best method appeared to be the reaction between sodium acetylenide and dialkyl-β-bromoethylamines in liquid ammonia. Although free dialkylaminoethyl bromides are exceedingly unstable (they dimerize markedly even at the temperature of dry ice), their use is more convenient than the use of their salts for that purpose described in the literature [5]. Dialkylaminoethyl chlorides under these conditions are practically unreactive. Other methods are known for synthesizing dialkylaminobutynes [6,7] but they are less convenient.

Synthesis of substituted 5-dialkylaminopentyn-3-ols (X-XVIII) was carried out using the Mannich reaction under the conditions worked out by us for preparation of substituted aminobutynols [1].

\* Communication I - see [1].

TABLE 1. Aminopentynols  $R_1R_2C(OH)C\equiv CCH_2CH_2N(Alk)_2$ .

Amino alcohol	$R_1$	$R_2$	$N(Alk)_2$	Yield, %	M. p.	Solvent for crystallization	N found, %	Empirical formula	N calc., %
I	$C_6H_5$	$C_6H_5$	$N(CH_3)_2$	97	160.5—161.5°	Isopropyl alcohol	4.90, 4.92	$C_{19}H_{21}ON$	5.01
II	$C_6H_5$	$C_6H_5$	$N(C_2H_5)_2$	95.5	103—104	Dibutyl ether	4.46, 4.74	$C_{21}H_{25}ON$	4.56
III	$C_6H_5$	$C_6H_5$	$N(CH_2)_5$	90	149—150	Dibutyl ether	4.40, 4.52	$C_{22}H_{25}ON$	4.39
IV	$C_6H_5$	$C_6H_{11}$	$N(CH_3)_2$	96	112—112.5	Petroleum ether (b.p. 60-80°)	5.15, 5.20	$C_{19}H_{27}ON$	4.91
V	$C_6H_5$	$C_6H_{11}$	$N(C_2H_5)_2$	90	59—60	Petroleum ether (b.p. 60-80°)	4.65, 4.73	$C_{21}H_{31}ON$	4.47
VI	$C_6H_5$	$C_6H_{11}$	$N(CH_2)_5$	95	123—124	Benzine (b.p. 100-150°)	4.28, 4.38	$C_{22}H_{31}ON$	4.30
VII	$C_6H_4-C_6H_4$		$N(CH_3)_2$	92	163—163.5	Dibutyl ether	5.09, 5.25	$C_{19}H_{19}ON$	5.05
VIII	$C_6H_4-C_6H_4$		$N(C_2H_5)_2$	95	132.5—133	Dibutyl ether	4.70, 4.74	$C_{21}H_{25}ON$	4.59
IX	$C_6H_4-C_6H_4$		$N(CH_2)_5$	96	150—151	Dibutyl ether	4.50, 4.59	$C_{22}H_{25}ON$	4.41

\* For the uncrystallized product.



It appeared that in this case the reaction proceeds only in presence of monovalent copper salts (in particular, copper acetylide). Use of the hydrobromides of diethylamine and piperidine gave better yields than use of hydrochlorides; the position was reversed for dimethylamine.

Nine substituted aminopentynols of this series were obtained: 1,1-diphenyl-5-dimethylaminopentyn-3-ol-1 (X), 1,1-diphenyl-5-diethylaminopentyn-3-ol-1 (XI), 1,1-diphenyl-5-piperidinopentyn-3-ol-1 (XII), 1-phenyl-1-cyclohexyl-5-dimethylaminopentyn-3-ol-1 (XIII), 1-phenyl-1-cyclohexyl-5-diethylaminopentyn-3-ol-1 (XIV), 1-phenyl-1-cyclohexyl-5-piperidinopentyn-3-ol-1 (XV), 1-dimethylamino-4-(9'-hydroxyfluorenyl-9')-butyne-2 (XVI), 1-diethylamino-4-(9'-hydroxyfluorenyl-9')-butyne-2 (XVII), 1-piperidino-4-(9'-hydroxyfluorenyl-9')-butyne-2 (XVIII), and also their hydrochlorides (Tables 2 and 3).

Tertiary propargylcarbinols used as initial compounds in the Mannich reaction were obtained by reacting propargylmagnesium bromides with ketones. The reaction was achieved similarly to that described for a series of aliphatic and alicyclic ketones [8]. In the literature, data is given on preparation of propargylcarbinols via organozinc [9, 10] and organoaluminum [9, 11] compounds. Three compounds were synthesized by the method indicated: 1,1-diphenylbutyn-3-ol-1, 1-phenyl-1-cyclohexylbutyn-3-ol-1, 9-hydroxy-9-(propyn-1'-yl-3')fluorene, the latter two carbinols being obtained for the first time.

#### EXPERIMENTAL

**Dimethyl- $\beta$ -bromoethylamine.** Dimethylbromoethylamine hydrobromide was obtained from dimethylaminoethanol [12]. To isolate the free base the salt was condensed with concentrated caustic soda solution, the alkaline solution being extracted three times with ether. The extract was briefly dried with potash and distilled in vacuo. The product was collected in a receiver cooled with a mixture of dry ice and alcohol. Yield of substance with b.p. 33-35° at 14 mm amounted 86%.

**Diethyl- $\beta$ -bromoethylamine.** Synthesized similarly to the previous compound. The free base was obtained in 91% yield, b.p. 44-48° at 4 mm or 49-52° at 11 mm.

**N-( $\beta$ -Bromoethyl)-piperidine.** Synthesized similarly to the two previous amines. Yield 93.5%, b.p. 83.5-86° at 11 mm.

TABLE 2  
Aminopentynols  $R_1R_2C(OH)CH_2C\equiv CCH_2N(Alk)_2$

Amino alcohol	$R_1$	$R_2$	$N(Alk)_2$	Yield, % <sup>•</sup>	M. p.	Solvent for crystallization	N found, %	Empirical formula	N calc., %
X	$C_6H_5$	$C_6H_5$	$N(CH_3)_2$	92	108–108.5° **	Dibutyl ether	5.04, 5.19	$C_{19}H_{21}ON$	5.01
XI	$C_6H_5$	$C_6H_5$	$N(C_2H_5)_2$	86	61.5–62.5	Petroleum ether (b.p. 10–80°)	4.49, 4.50	$C_{21}H_{25}ON$	4.56
XII	$C_6H_5$	$C_6H_5$	$N(C_2H_5)_2$	92.5	105.5–106.5	Benzine (b.p. 100–150°)	4.32, 4.47	$C_{22}H_{25}ON$	4.39
XIII	$C_6H_5$	$C_6H_{11}$	$N(CH_3)_2$	94.5	82.5–83.5	Petroleum ether (b.p. 60–80°)	4.92, 4.97	$C_{19}H_{27}ON$	4.91
XIV	$C_6H_5$	$C_6H_{11}$	$N(C_2H_5)_2$	90.5	—	—	4.60, 4.60 ***	$C_{21}H_{31}ON$	4.47
XV	$C_6H_5$	$C_6H_{11}$	$N(CH_3)_2$	93	—	—	4.42, 4.61 ***	$C_{22}H_{31}ON$	4.30
XVI	$C_6H_4-C_6H_4$	$C_6H_4$	$N(CH_3)_2$	83	155.5–156	Dibutyl ether	5.14, 5.25	$C_{19}H_{19}ON$	5.05
XVII	$C_6H_4-C_6H_4$	$C_6H_4$	$N(C_2H_5)_2$	83	158–158.5	Isopropyl alcohol, dibutyl ether	4.82, 4.86	$C_{21}H_{23}ON$	4.59
XVIII	$C_6H_4-C_6H_4$	$C_6H_4$	$N(CH_3)_2$	87	172.5–173.5	Dibutyl ether, ethyl alcohol	4.57, 4.60	$C_{22}H_{23}ON$	4.41

• For the product directly obtained from the reaction.

•• For this compound [4], m.p. indicated is 134°, but method of purification and proof of structure are not given. The method of synthesis, unlike ours, does not permit a definite estimate of the structure of the substance.

\*\*\* The product analyzed was that obtained directly from the reaction and carefully dried in vacuo.

TABLE 3

Hydrochlorides of Substituted Aminopentynols (I-XVIII)

Base	M. p.	Solvent for crystallization	Cl found, %	Empirical formula	Cl calc., %
I	165-165.5°	Isopropyl alcohol	11.39, 11.46	C <sub>19</sub> H <sub>21</sub> ON · HCl	11.23
II	176(decomp.)	Chloroform	10.33, 10.38	C <sub>21</sub> H <sub>25</sub> ON · HCl	10.31
III	201-203 (decomp.)	Chlorobenzene	9.63, 9.71	C <sub>22</sub> H <sub>25</sub> ON · HCl	9.96
IV	196.5-197 (decomp.)	Dichloroethane	10.79, 10.81	C <sub>19</sub> H <sub>27</sub> ON · HCl	11.02
V	163.5-164	Dioxan, dichloroethane	10.08, 10.09	C <sub>21</sub> H <sub>31</sub> ON · HCl	10.13
VI	172-173 (decomp.)	Dioxan	9.82, 9.84	C <sub>22</sub> H <sub>31</sub> ON · HCl	9.80
VII	202(decomp.)	Isopropyl alcohol	11.48, 11.49	C <sub>19</sub> H <sub>19</sub> ON · HCl	11.29
VIII	183-183.5	Isopropyl alcohol	10.50, 10.64	C <sub>21</sub> H <sub>23</sub> ON · HCl	10.37
IX	216-217	n-Butyl alcohol	9.93, 10.02	C <sub>22</sub> H <sub>23</sub> ON · HCl	10.02
X	218.5-219	Isopropyl alcohol	11.30, 11.31	C <sub>19</sub> H <sub>21</sub> ON · HCl	11.23
XI	214-215 (decomp.)	Isopropyl alcohol	10.34, 10.41	C <sub>21</sub> H <sub>25</sub> ON · HCl	10.31
XII	214.5-215	Dioxan, acetone	10.10, 10.16	C <sub>22</sub> H <sub>25</sub> ON · HCl	9.96
XIII	214-215	Isopropyl alcohol	11.04, 11.10	C <sub>19</sub> H <sub>27</sub> ON · HCl	11.02
XIV	160-161	Chlorobenzene	10.05, 10.07	C <sub>21</sub> H <sub>31</sub> ON · HCl	10.13
XV	195-196	Dioxan	9.82, 9.83	C <sub>22</sub> H <sub>31</sub> ON · HCl	9.80
XVI	195-195.5 (decomp.)	n-Butyl alcohol	11.34, 11.36	C <sub>19</sub> H <sub>19</sub> ON · HCl	11.29
XVII	238-238.5 (decomp.)	Ethyl alcohol	10.42, 10.43	C <sub>21</sub> H <sub>23</sub> ON · HCl	10.37
XVIII	202-203 (decomp.)	n-Butyl alcohol + ether	10.13, 10.15	C <sub>22</sub> H <sub>23</sub> ON · HCl	10.02

**4-Dimethylaminobutyne-1.** To a solution of sodium acetylenide (obtained from 7.3 g of sodium) in 300-400 ml of liquid ammonia, 32 g of dimethylaminoethyl bromide was added over a period of 5-10 minutes. The reaction mixture was stirred 4-5 hours, the amount of liquid ammonia being kept approximately constant, and then left overnight. On the following day the solid residue was wetted with ether and carefully dissolved in the smallest possible amount of water. The layers were separated, and the aqueous extracted several times with ether. After drying with potash and distillation, 7.75 g (38%) was obtained of a product with b.p. 104-110°. It was twice redistilled.

B.p. 107-109°,  $d_4^{20}$  0.7946,  $n_D^{20}$  1.4292. According to the data in the literature  $d_4^{25}$  0.8111,  $n_D^{25}$  1.4294 [6],  $d_4^{20}$  0.7892,  $n_D^{20}$  1.4290 [7].

**4-Diethylaminobutyne-1.** Obtained similarly in 80% yield.

B.p. 54.5-57.5° at 30 mm,  $d_4^{20}$  0.8045,  $n_D^{20}$  1.4366. According to the data in the literature  $d_4^{20}$  0.8031,  $n_D^{20}$  1.4388 [7].

**4-(N-Piperdino)-butyne-1.** Synthesized similarly in 80% yield.

B.p. 65-67° at 11 mm,  $d_4^{20}$  0.8916,  $n_D^{20}$  1.4735. According to the data in the literature  $d_4^{20}$  0.8837,  $n_D^{20}$  1.4740 [7].

**Substituted 5-Aminopentyn-2-ols (I-IX).** To a suspension of 0.05 g-mole of sodium amide in 50 ml of liquid ammonia, 0.04 g-mole of the corresponding dialkylaminobutyne was added over a period of 5 minutes. After ten minutes' stirring of the resulting solution or suspension, 0.045 g-mole of the ketone in 40 ml of absolute ether was added over a period of 5-10 minutes. The mixture was stirred until the ammonia had completely evaporated and then boiled with reflux condenser for 2 hours. On cooling, the solution was poured into a mixture of ice and hydrochloric acid, the ether layer separated and again extracted with dilute acid. The united acid extracts were rendered alkaline with ammonia solution and the resulting amino alcohol extracted with chloroform. Ether was used for extraction in synthe-

sis of compounds (IV), (V) and (VI). After drying with potash, the chloroform or ether was distilled off under water-jet pump vacuum, the residue being an almost colorless crystalline substance. The product was recrystallized several times (Table 1).

1,1-Diphenylbutyn-3-ol-1. To 2 g of magnesium filings activated by heating with iodine, 10 ml of absolute ether and 0.03 g of mercuric chloride was added ~0.4 g of propargyl bromide. A vigorous action began immediately. Then with stirring a solution of 4.6 g of propargyl bromide and 7 g of benzophenone in 25 ml of anhydrous benzene\* and 10 ml of ether was gradually added. Addition took place at such a rate that the mixture boiled gently continuously. On completion of the addition, stirring was continued for a further hour, and the reaction mixture poured into an ammonium chloride solution. The organic layer was separated, dried with magnesium sulfate, and the solvent distilled off in vacuo toward the end. Crude propargylcarbinol was obtained in nearly quantitative yield, calculated on the benzophenone (8.85 g with diphenylbutynol content 92.5%\*), and it crystallized on standing or on introducing a primer. After distillation in vacuo, 7.38 g (86.5%) was obtained of a product distilling at 143-148° and 2.5 mm. It crystallized immediately and had m.p. 62-63°. After several recrystallizations from petroleum ether (b.p. 60-80°), the compound melted at 64-65°. According to the data in the literature [11], b.p. 125-126° at 0.3 mm and m.p. 64-66°.

Found %: C 86.51, 86.80; H. 6.52, 6.62.  $C_{16}H_{14}O$ . Calculated %: C 86.46, H 6.34.

1-Phenyl-1-cyclohexylbutyn-3-ol-1. Obtained similarly to the previous compound, but without using benzene. After distillation, 81% of a viscous liquid was obtained, distilling at 139-143° (2 mm). The compound was distilled once more for analysis.

B.p. 143° at 2 mm,  $n_D^{20}$  1.5475.

Found %: C 84.37, 83.98; H 9.28, 9.11.  $C_{16}H_{20}O$ . Calculated %: C 84.16; H 8.85.

9-Hydroxy-9-(propyn-1'-yl-3')-fluorene. To 1 g of magnesium activated by heating with iodine, 10 ml of ether and 0.02 g of mercuric chloride was added several milliliters of a solution of 3.3 g of propargyl bromide in 20 ml of absolute ether. When the reaction began, the flask was cooled with an ice-salt mixture and the remaining bromide solution added with vigorous stirring over a period of 10-15 minutes. On cooling, the reaction mixture was stirred for a further half-hour, and then a solution of 4 g of fluorenone in 15-20 ml of absolute ether added over a period of 5 minutes. The yellow fluorenone color disappeared almost immediately, and a voluminous gray precipitate separated out. To complete the reaction, stirring was continued for 30 minutes, and the reaction mixture then decomposed with ammonium chloride solution. The ether layer was separated and dried with magnesium sulfate. After removal of solvent, a solid product remained (4.97 g); recrystallizing it from benzine (b.p. 100-150°) gave 4.42 g (90.5%) of a substance with m.p. 99-101°. Further recrystallizations from the same solvent and then from petroleum ether (b.p. 60-80°) allowed raising of the m.p. 104-105°.

Found %: C 87.42, 87.50; H 5.79, 5.79.  $C_{16}H_{12}O$ . Calculated %: C 87.29; H 5.50.

An attempt at using in the synthesis of this carbinol the simpler method used for preparation of the previous two compounds did not give positive results. The precipitate of the intermediate complex settling out isolated the magnesium, and the reaction ceased.

Preparation of Substituted 5-Aminopentyn-3-ols (X-XVIII). A mixture of 1 g of substituted propargylcarbinol, 0.45 g of dimethylamine hydrochloride (or, respectively, 0.75 and 0.80 g of diethylamine hydrobromide and piperidine hydrobromide), 1.5 ml of formalin, 0.01 g of ground copper acetylenide and 5 ml of alcohol was heated on a boiling water bath for 4 hours. On cooling, the reaction mixture was poured into water slightly acidified with hydrochloric acid, and a substance of nonbasic character was extracted with ether. The aqueous solution was rendered alkaline, the resulting amino alcohol extracted with ether, substances (XVI-XVIII)—with chloroform. The extract was dried with potash, the solvent then distilled off in vacuo. A colorless crystalline substance remained, which was recrystallized from a suitable solvent until melting point was constant. Compounds (XIV) and (XV) did not crystallize even on prolonged standing (Table 2).

\*Use of ether only as the solvent in the synthesis did not allow preparation of a satisfactory yield, because by carrying out the reaction in this way an intermediate complex settled out which coated the magnesium, the reaction ceasing; the complex was soluble in the ether-benzene mixture.

••Determination of the primary acetylene group was carried out by a well-known method [13].

**Hydrochlorides of Amino Alcohols.** A solution of the base in ether, acetone, or ethanol was treated with alcoholic hydrogen chloride solution. From ether the salt precipitated immediately; from acetone and alcohol it had to be precipitated with ether in most cases. The hydrochloride was filtered off and recrystallized from a suitable solvent (Table 3).

#### SUMMARY

1. A convenient method was found for synthesizing 4-dialkylaminobutynes-1.
2. A method was evolved for synthesizing 1,1-disubstituted 5-dialkylaminopentyn-2-ols-1, based on reaction of sodium derivatives of dialkylaminobutynes with ketones. Nine compounds of this series not described in the literature were obtained, and also their hydrochlorides.
3. Convenient methods were found for synthesizing aryl-substituted tertiary propargylcarbinols and three representatives of this group of compounds obtained, two of which had not been described in the literature.
4. Using the Mannich reaction, from tertiary propargylcarbinols nine 1,1-disubstituted 5-dialkylaminopentyn-3-ols-1 were obtained, eight of which had not been described in the literature, and their hydrochlorides.

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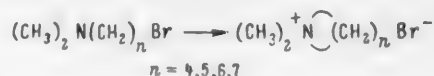
# INVESTIGATION IN THE FIELD OF FORMATION OF POLYMETHYLENEAMMONIUM RINGS

## I. SYNTHESIS AND CONVERSIONS OF SEVERAL ESTERS OF DIPEHNYLACETIC ACID

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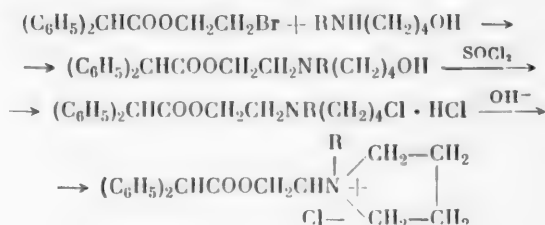
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Many substances containing a quaternary ammonium group are active acetylcholine antagonists. However, their action on the central nervous system is slight, which explains the poor penetration of these compounds into the central nervous system. With this in mind, it appeared of interest to prepare such cholinolytic substances, the amino group of which would be converted into a quaternary one under the conditions existing in the organism. It is known that  $\omega$ -halotrialkylamines in an alkaline medium undergo cyclization, forming dialkylcyclopolymethyleneammonium halides. Cyclization of  $\omega$ -bromoalkyldimethylamine serves as an example of a similar conversion [1]:



It appeared probable that cholinolytic compounds containing an  $\omega$ -haloalkyl group at the tertiary nitrogen on introduction into the organism would undergo a similar conversion, forming quaternary ammonium cholinolytics. Since the rate of similar conversion depends on the nature of the halogen, length of carbon chain, substituents at the nitrogen, etc., it should be possible to prepare compounds capable of being converted into quaternary ones after entering the central nervous system.

With the aim of preparing such compounds, we have synthesized several tertiary aminoethyl esters of diphenylacetic acid, on the cyclization of which are formed quaternary derivatives of pyrrolidylethyl esters of diphenylacetic acid. The latter are known to be substances possessing definite cholinolytic action [2]. Synthesis of these compounds and their conversion were carried out according to the scheme:



The majority of the 1,4-amino alcohols chosen for synthesis had not been described in the literature. Two possible paths were open for preparation of similar amino alcohols: firstly, reaction of 1,4-halogenhydrins with amines, and secondly, reduction of N-alkylamides of  $\beta$ -carboxypropionic acid:



N-Ethylaminobutanol-4 was obtained by us by both of the methods indicated. In this case it appeared that the

TABLE 1  
Amino Alcohols  $\text{R}_1\text{HNCHCH}_2\text{CH}_2\text{CHOH}$   
 $\text{R}_2$

R	Reaction conditions*				Aminoal- cohol		B. p. (pres- sure in mm)	n <sub>D</sub> <sup>20</sup>	d <sub>4</sub> <sup>20</sup>	MR <sub>D</sub>		Empirical formula	% N	
	R <sub>1</sub>	R <sub>2</sub>	amine/ chlorohy- drin ratio	temper- ature	time, hr	yield, %				found	calc.		found	calculated
CH <sub>3</sub>	H	H	5:1	80°	16	52	87 <sup>(10)</sup>	1.4530	0.9184	30.46	30.49	C <sub>3</sub> H <sub>13</sub> ON	13.40, 13.46	13.58
C <sub>2</sub> H <sub>5</sub>	H	H	5:1	70	20	64	86 <sup>(7)</sup> **	1.4521	0.9120	34.70	35.14	C <sub>6</sub> H <sub>15</sub> ON	12.16, 12.17	11.95
n-C <sub>3</sub> H <sub>7</sub>	H	H	2.5:1	100	12	44	79 <sup>(4)</sup>	1.4532	0.8982	39.79	39.82	C <sub>7</sub> H <sub>17</sub> ON	10.73, 10.80	10.68
iso-C <sub>3</sub> H <sub>7</sub>	H	H	3:1	80	20	42	89 <sup>(6)</sup>	1.4512	0.8890	39.74	39.82	C <sub>7</sub> H <sub>17</sub> ON	10.61, 10.76	10.68
CH <sub>3</sub>	H	CH <sub>3</sub>	5:1	100	10	40	70-72 <sup>(6)</sup>	1.4502	0.9037	34.85	35.12	C <sub>6</sub> H <sub>15</sub> ON	11.68, 11.88	11.95
C <sub>2</sub> H <sub>5</sub>	H	CH <sub>3</sub>	5:1	100	10	52	74 <sup>(5)</sup> ***	1.4486	0.8889	39.57	39.77	C <sub>7</sub> H <sub>17</sub> ON	10.70, 10.84	10.68
CH <sub>3</sub>	CH <sub>3</sub>	H	4:1	70	30	25	96 <sup>(11)</sup>	1.4550	0.9150	34.77	35.12	C <sub>6</sub> H <sub>15</sub> ON	11.90, 12.14	11.95
C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	H	5:1	70	30	36	75 <sup>(4)</sup>	1.4521	0.8970	39.48	39.77	C <sub>7</sub> H <sub>17</sub> ON	10.94, 10.98	10.68

\* See EXPERIMENTAL.

\*\* Data in the literature [3]: b.p. 76° (1.5 mm), n<sub>D</sub><sup>20</sup> 1.4548, d<sub>4</sub><sup>10</sup> 0.9120.

\*\*\* Data in the literature [4]: b.p. 108° (20 mm), n<sub>D</sub><sup>25</sup> 1.4458.

TABLE 2

Hydrochlorides of Alkyl-( $\delta$ -chloroalkyl)-aminoethyl Esters of Diphenylacetic Acid $(C_6H_5)_2CHCOOCH_2CH_2NCHCH_2CH_2CHCl \cdot HCl$ 

$$\begin{array}{c} R_1 \\ | \\ R_2 \end{array}$$

Compound	R	R <sub>1</sub>	R <sub>2</sub>	Yield, %	Solvent for crystallization	M. p.	Found, %		Empirical formula	Calculated, %	
							C	H		C	H
I	CH <sub>3</sub>	H	H	62	Acetone + ether	103°	63.71	63.80	C <sub>21</sub> H <sub>26</sub> O <sub>2</sub> NCl · HCl	63.62	6.86
II	C <sub>2</sub> H <sub>5</sub>	H	H	54	Acetone	124—125	64.32	7.40	C <sub>22</sub> H <sub>28</sub> O <sub>2</sub> NCl · HCl	64.40	7.12
III	n-C <sub>3</sub> H <sub>7</sub>	H	H	58	Acetone + ether	84	64.80	7.46	C <sub>23</sub> H <sub>30</sub> O <sub>2</sub> NCl · HCl	65.03	7.36
IV	iso-C <sub>3</sub> H <sub>7</sub>	H	H	45	Acetone + ethyl acetate	124	64.94	7.62	C <sub>23</sub> H <sub>30</sub> O <sub>2</sub> NCl · HCl	65.03	7.36
V	CH <sub>3</sub>	H	CH <sub>3</sub>	68	Benzene; acetone + ether	120—121	64.30	6.84	C <sub>22</sub> H <sub>28</sub> O <sub>2</sub> NCl · HCl	64.40	7.12
VI	C <sub>2</sub> H <sub>5</sub>	H	CH <sub>3</sub>	72	Ethyl acetate	91—92	65.20	7.68	C <sub>23</sub> H <sub>30</sub> O <sub>2</sub> NCl · HCl	65.03	7.36
VII	CH <sub>3</sub>	CH <sub>3</sub>	H	61	Does not crystallize	—	—	—	—	—	—
VIII	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	H	60	The same	—	—	—	—	—	—

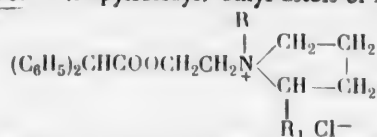
first of them, i.e., reaction of 1-chlorobutanol-4 with ethylamine, is experimentally simpler and gives a better yield of the desired amino alcohol. Therefore, all the remaining amino alcohols (Table 1) were obtained by reacting the corresponding amine with the 1, 4-halogenhydrin (1-chlorobutanol-4, 1-chloropentanol-4 and 4-chloropentanol-1).

The relative low yields of the basic reaction products (40-60%) can evidently be explained by cyclization of the 1,4-halogenhydrins into tetrahydrofuran derivatives along with the basic reaction. This unwanted process could be avoided by employing not the halogenhydrins themselves, but their acyl derivatives. However, reaction of 1-acetoxy-4-chlorobutane with the amine and subsequent splitting off of the acetyl group, giving high yields of 1-dialkylaminobutanol-4 [5, 6], did not lead to the desired results in the case of monoalkyl derivatives. The reaction product was a difficultly separable mixture of the desired amino alcohol and other compounds, the structure of which was not determined. The particularly low yield of 4-N-alkylaminopentanol-1 was evidently connected with the low activity of the chlorine at the secondary carbon atom. It should be noted that an attempt to obtain 4-diethylaminopentanol-1 by a similar reaction was unsuccessful [7].

On reacting the resulting amino alcohols with the 2-bromoethyl ester of diphenylacetic acid  $\delta$ -hydroxydialkylaminoethyl esters of this acid were formed, which were directly converted into hydrochlorides of the  $\delta$ -chloro derivatives (Table 2). Purification and isolation of the latter were very difficult owing to the fact that these compounds crystallized very slowly.

On rendering alkaline aqueous solutions of compounds (I-VIII), the bases of these substances were obtained as oils insoluble in water. On heating benzene solutions of the bases, the latter were gradually cyclized, forming quaternary compounds—chloroalkylates of  $\beta$ -(N-pyrrolidyl)-ethyl esters of diphenylacetic acid (Table 3).

Tertiary compounds (V) and (VII), and also (VI) and (VIII), formed the same quaternary products (XIII) and (XIV), respectively. Compound (IX) was also obtained by counter synthesis by reacting the  $\beta$ -chloroethyl ester of diphenylacetic acid with N-methylpyrrolidine.

TABLE 3. Chloroalkylates of  $\beta$ -(N-pyrrolidyl)-ethyl Esters of Diphenylacetic Acid

Compound	R	R <sub>1</sub>	Yield %	Solvent for crystallization	M. p.	Cl found, %	Empirical formula	Cl calc., %
IX	CH <sub>3</sub>	H	75	Isoamyl alcohol + ether	51°	9.94, 10.11	C <sub>21</sub> H <sub>26</sub> O <sub>2</sub> NCl	9.85
X	C <sub>2</sub> H <sub>5</sub>	H	86	Acetone	51–52	9.48, 9.49	C <sub>22</sub> H <sub>28</sub> O <sub>2</sub> NCl	9.48
XI	n-C <sub>3</sub> H <sub>7</sub>	H	69	Methyl ethyl ketone	153–154	9.23, 9.24	C <sub>23</sub> H <sub>30</sub> O <sub>2</sub> NCl	9.14
XII	iso-C <sub>3</sub> H <sub>7</sub>	H	70	Acetone	91–92	9.00, 8.92	C <sub>23</sub> H <sub>30</sub> O <sub>2</sub> NCl	9.14
XIII	CH <sub>3</sub>	CH <sub>3</sub>	72	Butanol + ether	189 (decomp)	9.51, 9.53	C <sub>22</sub> H <sub>28</sub> O <sub>2</sub> NCl	9.48
XIV	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	70	Acetone	148–149	9.03, 9.07	C <sub>23</sub> H <sub>30</sub> O <sub>2</sub> NCl	9.14

Yields of quaternary compounds varied between 70 and 85%. This, however, was connected with the losses of the substances during isolation; in the case of cyclization of compounds (III) and (V) it was shown that their bases, on heating in alcohol, are converted into quaternary derivatives (XI) and (XIII) in quantitative yield.

Having in mind quantitative conversion of the bases of compounds (I–VIII) into quaternary compounds, we attempted a study of the kinetics of this conversion. It should be indicated that when the kinetics of the cyclization of the primary (and partially of the secondary) halobutylamines was being studied in detail [8–10], corresponding quantitative data on conversion of dialkylaminobutyl chlorides was not at hand. There are only indications that the individual compounds can be converted [1, 11–13].

TABLE 4: Constants for Cyclization Rate of Bases of Compounds (I–VI) (96% ethanol, 20°)

	Base of compound					
	I	II	III	IV	V	VI
k	0.22	0.17	0.091	0.033	0.0020	0.00063

Investigations on the cyclization of compounds (I–VI) were carried out by us in 96% ethanol in presence of excess sodium ethylate. Reaction rate was determined by change in chloride ion concentration. As would be expected, reaction rate was independent of both concentration and amount of sodium ethylate (if the amount of the latter was greater than 1 mole per 1 mole of the substance). The reaction conformed to the equation of a first order reaction. Calculated constants for the reaction rate for bases of compounds (I–VI) are given in Table 4.

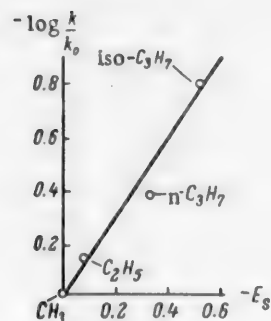
As seen from the data of Table 4, gradual increase in size and branching of the radical attached to the nitrogen in compounds (I–IV) leads to decrease in rate of cyclization of the corresponding bases. It was logical to propose that in this instance decrease in rate depends on a steric factor—radical volume. We attempted to apply to the constants for the rates of cyclization one of the equations of Taft, characterizing the dependence of reaction rate on a steric factor [14]:

$$\log\left(\frac{k}{k_0}\right) = \rho E_s$$

where  $k_0$  is the constant for the reaction rate for a compound with a methyl radical;  $k$  is the rate constant for a homologous compound with another radical;  $E_S$  is the steric constant characterizing a given radical (for values of  $E_S$ , see [14]);  $\delta$  is the coefficient for the given reaction at the given temperature.

From the figure it is seen that there is satisfactory agreement between the values found for the constants and values of the  $E_S$  constants. The incomplete agreement is evidently caused by the fact that other factors beside steric ones exert an influence on cyclization rate, for instance, differences in the nucleophilic properties of the nitrogen atom in these compounds.

The observed compliance of cyclization rates with Taft's equation is of interest from two points of view. Firstly, although the applicability of Taft's equation to alkylation of tertiary amines was well known [14-15], the present instance is specific, in that ring closure occurs simultaneously with alkylation. On the other hand, use of Taft's equation renders possible preliminary calculation of the cyclization rate of other similar compounds.



Conformity of cyclization rates with Taft's equation.

In the study of the kinetics of conversion in water. In actual fact, we dealt with cyclization of the compounds not in water but in substance-water and water-substance emulsions. Naturally, in this case reaction rate depended on the relative amounts of water and substance. Thus, on diluting 10 times, the rate constant increased 1.25-1.3 times. For this reason, we evaluated only approximately the conversion rate of the bases of compounds (I-VI) in a fixed ratio of water and substance (Table 5).

As far as the cyclization rates of the bases of compounds (V) and (VI) are concerned, in this case the marked decrease in reaction rates is caused by the replacement of the chlorine at the primary carbon by a chlorine at the secondary carbon.

It should be noted that, notwithstanding the marked decrease in reaction rate, the character of the effect of replacing the methyl radical attached to the nitrogen by an ethyl one in compounds (I), (II) and (V), (VI) (Table 4) remains the same.

Besides investigating the kinetics of cyclization in alcohol, we attempted a study of the rate of this conversion in water. This was of interest from the point of view of the behavior of the substances in an organism. However, because of the poor solubility of the bases of compounds (I-VI) in water, we were unsuccessful

TABLE 5. Polycyclization period  $\tau$  in Aqueous Emulsion at 36° (10<sup>-4</sup> g-mole of compound in 10 ml of water)

	Base of compound					
	I	II	III	IV	V	VI
$\tau$ , min	1.8	3.5	7	25	360	870

From the data of Table 5 it is seen that in cyclization in aqueous emulsion the character of the influence of radicals and nature of halogen on reaction rate remains unchanged.

## EXPERIMENTAL

1-Chlorobutanol-4 was obtained [16] in 70-75% yield. 1-Chloropentanol-4 was obtained [4] in 74% yield. 1-Acetoxy-pentanol-4 was obtained by hydrogenating 1-acetoxypentanone-4 in presence of Raney nickel at the usual temperature and pressure in 90% yield [4].

1-Acetoxy-4-chloropentane. To a solution cooled to -10° of 22 g of 1-acetoxypentanol-4 and 11.8 g of pyridine in 50 ml of absolute ether was added with stirring a solution of 9 g of thionyl chloride in 15 ml of ether. The

precipitate settling out was filtered off, to the filtrate a further 9 g of thionyl chloride added. Ether was distilled off and the residue heated for 1.5 hours at 70-75° and then distilled, the fraction with b.p. 77-85° (10 mm) being collected. In a repeat distillation, 1-acetoxy-4-chloropentane boiled at 78-79° (8 mm),  $n_D^{20}$  1.4330. Yield 15.1 g (61%). According to the data in the literature [4,17], b. p. 96-98° (18 mm),  $n_D^{20}$  1.4336.

**4-Chloropentanol-1.** To a solution of 21 g of 1-acetoxy-4-chloropentane in 40 ml of methanol was added 5 ml of a 30% solution of hydrogen chloride in methanol and the solution boiled for 2 hours. Alcohol was then distilled off and the residue distilled in vacuo. Yield of 4-chloropentanol-1 14.4 g (92%). B.p. 77-79° (10 mm),  $n_D^{20}$  1.4490. According to the data in literature [17], b.p. 76-79° (9 mm),  $n_D^{20}$  1.4530.

**Reaction of 1,4-Halohydrins with Amines (Table 1).** 0.2 g-mole of halohydrin and a 2-5-fold excess of amine were heated in a sealed ampoule. When the reaction was complete, excess amine was distilled off and the viscous residue washed with ether. Then to the residue was added a solution of 12 g of caustic potash in 10 ml of water, the solution saturated with potash and extracted with ether. The ether extract was dried with potash, ether distilled off and the product distilled in vacuo.

On carrying out the reaction with methylamine, methyl alcohol was used as the solvent, and the resulting N-methylamino alcohols extracted with benzene, not ether.

**N-Ethylamide of  $\beta$ -Carbethoxypropionic Acid.** To a solution of 0.2 g-mole of ethylamine in 25 ml of absolute ether was added with stirring at a temperature of 3-5° 0.1 g-mole of the acid chloride of  $\beta$ -carbethoxypropionic acid in 25 ml of ether. After adding all the solution, the mixture was heated to 25°, the precipitate settling out separated and twice washed with ether. Ether was distilled from the filtrate and the residue distilled in vacuo. B.p. 132° (4 mm). On cooling, the product crystallized. After two crystallizations from ether (with freezing) the product melted at 37-38°. Yield 15.3 g (88%).

Found %: N 8.28, 7.94.  $C_8H_{15}O_3N$ . Calculated %: N 8.09.

**1-Ethylaminobutanol-4.** To a solution of 0.25 g-mole of lithium alumohydride in 250 ml of ether was added at 20° 0.1 g-mole of the N-ethylamide of  $\beta$ -carbethoxypropionic acid in 100 ml of ether. After boiling for two hours, to the solution was added excess 40% caustic soda solution, the ether layer separated and dried with potash. After distilling off the ether, 1-N-ethylaminobutanol was distilled in vacuo. Yield 4.1 g (35%).

#### Esters of Diphenylacetic Acid

**$\beta$ -Bromoethyl Ester of Diphenylacetic Acid.** To a solution of 0.05 g-mole of diphenylacetic acid and 0.1 g-mole of ethylenebromohydrin in 70 ml of benzene were added 4 drops of concentrated sulfuric acid and the mixture boiled in an apparatus fitted with a water-separator. Separation of water was practically complete after 3-4 hours. The benzene solution was washed with soda solution and dried with sodium sulfate. After distillation of benzene, the product was distilled in vacuo. Yield of product 11.3 g (70%), b.p. 168-170° (2 mm). According to the data in the literature [18], b.p. 136-140° (0.002 mm).

$\beta$ -Chloroethyl Ester of Diphenylacetic Acid was obtained similarly; yield 75%; b.p. 181-183° (5 mm). According to the data in the literature [19], b.p. 130-135° (0.01 mm).

**Hydrochlorides of Alkyl-( $\delta$ -chloroalkyl)-aminoethyl Esters of Diphenylacetic Acid (Table 2).** To a solution of 0.02 g-mole of the 2-bromoethyl ester of diphenylacetic acid in 20 ml of toluene was added 0.04 g-mole of amino alcohol and the solution boiled for 3 hours. After cooling, the amino acid hydrobromide settling out as a precipitate or a viscous oil was separated and the toluene layer washed with 5 ml of water. The toluene layer was then extracted several times with 10% hydrochloric acid. The acid extracts were washed with ether and, with cooling, ammonia added until an alkaline reaction was given. The resulting oil was extracted with 50 ml of ether. The ether layer was dried with sodium sulfate, filtered, and the ether distilled off from the small weighed flask. The resulting  $\delta$ -hydroxydialkylaminoethyl ester of diphenylacetic acid was dissolved in 15 ml of anhydrous chloroform and to it with stirring at a temperature -5-0° a solution of the equivalent amount of thionyl chloride in 15 ml of chloroform added. The addition took 3-4 hours. Then, not heating the solution above 40°, the chloroform was distilled off in vacuo. 10 ml of anhydrous benzene was added and distilled off. This operation was repeated twice. The viscous precipitate was dissolved in 20 ml of anhydrous acetone, a little wood charcoal added, and boiled with reflux condenser for 2 minutes. After filtration, the solution was evaporated to a volume of 7-10 ml and absolute ether added until a slight turbidity appeared. After some time (up to two days) crystals precipitated. They were separated and recrystallized several times.



Chloroalkylates of  $\beta$ -(N-Pyrrolidyl)-ethyl Esters of Diphenylacetic Acid (Table 3). 1 g of the hydrochloride of the alkyl-( $\delta$ -chloroalkyl)-aminoethyl ester of diphenylacetic acid was dissolved in 10 ml of water and, with cooling, excess aqueous ammonia solution added. The resulting oil was quickly extracted with 30-50 ml of benzene and the benzene solution boiled in an apparatus fitted with a water-separator. The quaternary compound precipitated in an amount depending on time of boiling and took the form of crystals or an oil insoluble in benzene, solidifying on cooling. It was separated and recrystallized. To obtain compounds (IX-XII), the solution was boiled for 3-4 hours; for compounds (XIII-XIV), reaction time was increased to 10-12 hours.

Chloromethylate of  $\beta$ -(2'-Methylpyrrolidyl)-ethyl Ester of Diphenylacetic Acid (XIII). To a solution of 0.41 g of the hydrochloride of the N-methyl-(N-chloropentyl)-aminoethyl ester of diphenylacetic acid (V) in 20 ml of anhydrous alcohol was added a solution 0.023 g of sodium in 10 ml of alcohol and the mixture boiled with reflux condenser for 4 hours. The precipitate was separated and the filtrate evaporated to dryness. Yield of compound (XIII) was quantitative. M.p. 187-188°. After crystallizing from a mixture of butanol and ether the product melted at 189°.

Chloromethylate of  $\beta$ -(N-Pyrrolidyl)-ethyl Ester of Diphenylacetic Acid (IX). 2.74 g of the  $\beta$ -chloroethyl ester of diphenylacetic acid and 0.85 g of N-methylpyrrolidine were heated in an ampoule for 10 hours at 80°. The solid product obtained on cooling was washed with ether and crystallized twice from a mixture of isoamyl alcohol and ether. Yield 2.6 g (72%). M.p. 49-50°. A sample mixed with product (IX), obtained by cyclization of compound (I), gave no melting point depression.

Determination of Cyclization Reaction Constant.  $1 \cdot 10^{-4}$  g-mole of the substance was dissolved in 5 ml of 96% ethanol and placed in a TS-15 thermostat. To the alcoholic solution was added  $1.5 \cdot 10^{-4}$  g-mole of sodium ethylate (3 ml of 0.05 M solution in alcohol). After a definite interval of time, to the solution was added 5 ml of nitric acid (1:2), and the chloride ion concentration then determined by argentometric titration (by the method of Follgard), using 0.05 M solutions. The constants given in Table 4 are the averages of 6-10 determinations, experimental error  $\pm 2.5\%$ .

Determination of the cyclization constant in aqueous emulsions was carried out similarly.

#### SUMMARY

Synthesis was achieved of a series of derivatives of aminoethyl esters of diphenylacetic acid containing N- $\delta$ -chlorobutyl and N- $\delta$ -chloropentyl radicals. It was shown that similar compounds are converted to pyrrolidinium derivatives, and the kinetics of this conversion were investigated. It was shown that Taft's equation is applicable to the cyclization constants of the homologous series of these compounds.

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# INVESTIGATIONS IN THE FIELD OF QUINONES

## XXXVL. CONDENSATION OF IMINES OF ACETYLACETONE WITH p-BENZOQUINONE

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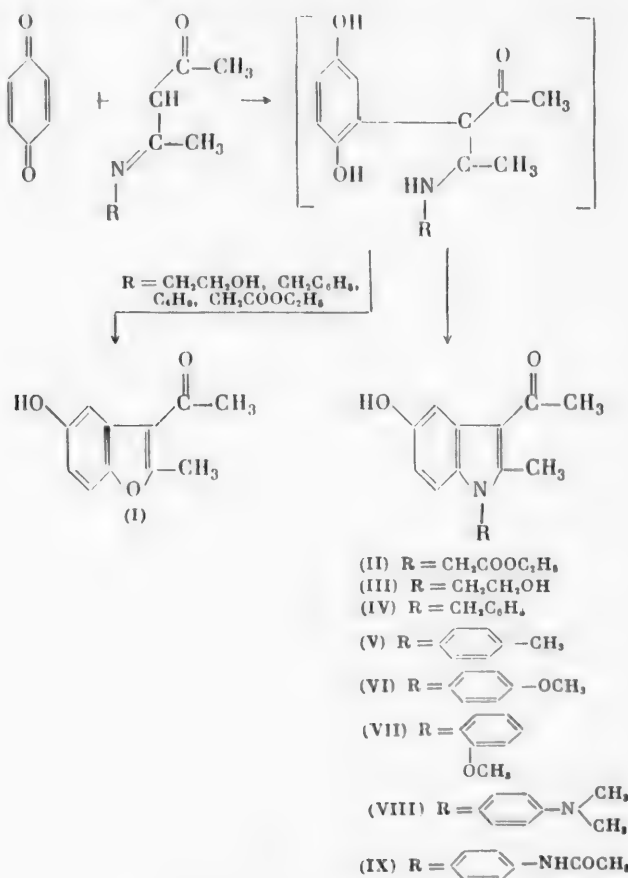
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 7,

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We have shown [1-4] that, depending on the nature of the quinone and imine, the condensation of p-quinones with imines of acetylacetone may give benzofuran derivatives or substituted indoles.

In the present work we investigated the reaction of p-benzoquinone with imines of acetylacetone containing various substituents on the nitrogen of the imino group. Condensation of p-benzoquinone with the N-butyl imine of acetylacetone leads to the formation of a benzofuran derivative (I). When other imines containing an aliphatic substituent ( $\text{CH}_2\text{COOC}_2\text{H}_5$ ,  $\text{CH}_2\text{CH}_2\text{OH}$ ,  $\text{CH}_2\text{C}_6\text{H}_5$ ) on the nitrogen react with p-benzoquinone, a mixture of substituted benzofuran (I) and derivatives of 5-hydroxyindole (II, III and IV) is formed. With aromatic substituents at the nitrogen of the imino group, imines of acetylacetone react with p-benzoquinone, forming only N-aryl-5-hydroxyindoles (V-IX). N-Aryl imines of acetylacetone with a negative substituent ( $\text{NO}_2$ , Br) in the para position of the phenyl ring form an exception. These imines do not react with p-benzoquinone.



It is of interest to compare data on the effect of various substituents at the nitrogen of the imino group on the direction of condensation with the basicity of the amines forming the corresponding imines of acetylacetone. Imines obtained from highly basic amines (pK 3-3.4) react with p-benzoquinone to form benzofuran derivatives. Imines obtained from amines of medium basicity (pK 4.6-5) form a mixture of indole and benzofuran derivatives. Aryl imines of acetylacetone obtained from less basic amines (pK 8-10) react with p-benzoquinone to form only 5-hydroxyindole derivatives. Therefore, the direction of condensation of p-benzoquinone with imines of acetylacetone is determined by the basicity of the amines forming the acetylacetone imines.

To determine the effect of the nature of the substituent at the nitrogen of the imine on the direction of condensation of p-benzoquinone with imines of acetylacetone, all experiments were carried out under the same conditions.

The corresponding 5-methoxyindole derivatives (X-XVII) were obtained by methylation of the 5-hydroxyindole derivatives (II-IX) with dimethyl sulfate.

#### EXPERIMENTAL

**2-Methyl-3-acetyl-5-hydroxybenzofuran (I).** A solution of 5.35 g of p-benzoquinone in 125 ml of dichloroethane was added gradually to a solution of 9.6 g of N-butyl imine of acetylacetone in 25 ml of dichloroethane in a Wurtz flask heated on the water bath. When the p-benzoquinone had been added, heating of the reaction solution on the water bath was continued, 100 ml of the solvent being distilled in 1 hour. The reaction solution was cooled, the precipitated crystals were filtered, washed with ether and recrystallized from methanol. The yield of the benzofuran derivative (I) was 3.7 g (39%), the m.p. was 232-233°. According to literature data, the m.p. is 234° [5]. A mixed melt with a sample of compound (I) obtained previously [5] showed no depression of the melting point.

**Condensation of p-benzoquinone with N-methylene carbethoxy imine of acetylacetone.** Under the same experimental conditions we obtained 10.6 g of a substance (with a wide melting point range) from 16.7 g of N-methylene carbethoxy imine of acetylacetone in 50 ml of dichloroethane and 10 g of p-benzoquinone in 250 ml of dichloroethane. Fractional recrystallization of the product from methanol gave 4 g of the ethyl ester (2-methyl-3-acetyl-5-hydroxyindolyl-1)-acetic acid (II); the m.p. was 220-221°.

Found %: C 65.06, 65.27; H 6.00, 6.27.  $C_{15}H_{17}O_4N$ . Calculated %: C 65.44; H 6.22.

The methanol mother liquor was diluted with water. The precipitated crystals were dried and recrystallized twice from benzene. We obtained 1.2 g of 2-methyl-3-acetyl-5-hydroxybenzofuran (I) with a m.p. of 232-233°. A mixed melt with a sample of the compound obtained previously [5] showed no depression of the melting point.

The condensation of p-benzoquinone with other imines of acetylacetone was carried out in a similar way. The results obtained are given in Table 1.

**Ethyl ester of (2-methyl-3-acetyl-5-methoxyindolyl-1)-acetic acid (X).** 5 ml of 2 N caustic soda in 1.27 g of dimethyl sulfate was added to a suspension of 1.36 g of hydroxyindole (II) in 4 ml of dioxan. The reaction mixture was shaken in a sealed vessel for 1 hour and was then diluted with two volumes of water. The precipitate obtained was filtered and washed with water. The yield of methoxyindole (X) was 0.9 g (63%); the m.p. was 113-114° [from a mixture of benzene and petroleum ether(1:2)].

Found %: C 66.23, 66.39; H 6.78, 6.48.  $C_{16}H_{19}O_4N$ . Calculated %: C 66.43; H 6.57.

The results of the methylation of other 5-hydroxyindole (III-IX) are given in Table 2.

#### SUMMARY

1. It was shown that condensation of p-benzoquinone with imines of acetylacetone having aliphatic substituents on the nitrogen leads to a benzofuran derivative or a mixture of derivatives of indole and benzofuran. Condensation of p-benzoquinone with N-aryl amines of acetylacetone containing primary substituents [ $CH_3$ ,  $OCH_3$ ,  $N(CH_3)_2$ ,  $HNCOCH_3$ ] in the benzene ring leads exclusively to indole derivatives. N-Aryl imines of acetylacetone with negative substituents in the benzene ring (Br,  $NO_2$ ) do not react with p-benzoquinone.

2. It was established that the basicity of the amine taking part in the formation of the imine has an essential influence on the direction of the condensation of p-benzoquinone with imines of acetylacetone.

TABLE 1

Condensation of p-Benzoquinone with Imines of Acetylacetone

Initial acetylacetone imine		p-Benzoquinone, g	Dichloroethane for dissolution, ml		Substances obtained
compound	amount, g		imine	quinone	
N-Butyl imine of acetylacetone	9.6	5.35	25	125	2-Methyl-3-acetyl-5-hydroxybenzofuran (I)
N-Methylene carbethoxy imine of acetylacetone	16.7	10	50	250	Ethyl ester of (2-methyl-3-acetyl-5-hydroxyindolyl-1)-acetic acid (II) 2-Methyl-3-acetyl-5-hydroxybenzofuran (I)
N-( $\beta$ -Hydroxyethyl)-imine of acetylacetone	26.7	16.2	75	375	1-( $\beta$ -Hydroxyethyl)-2-methyl-3-acetyl-5-hydroxyindole (III) 2-Methyl-3-acetyl-5-hydroxybenzofuran (I)
N-Benzyl imine of acetylacetone	59	27	100	500	1-Benzyl-2-methyl-3-acetyl-5-hydroxyindole (IV) 2-Methyl-3-acetyl-5-hydroxybenzofuran (I)
N-(p-Tolyl) imine of acetylacetone	23.6	10.8	50	250	1-(p-Tolyl)-2-methyl-3-acetyl-5-hydroxyindole (V)
N-(p-Methoxyphenyl)-imine of acetylacetone	25.6	10.8	50	250	1-(p-Methoxyphenyl)-2-methyl-3-acetyl-5-hydroxyindole (VI)
N-(o-Methoxyphenyl)-imine of acetylacetone	8.2	3.46	16	80	1-(o-Methoxyphenyl)-2-methyl-3-acetyl-5-hydroxyindole (VII)
N-(p-Dimethylamino-phenyl)-imine of acetylacetone	6.8	2.7	13	80	1-(p-Dimethylamino-phenyl)-2-methyl-3-acetyl-5-hydroxyindole (VIII)
N-(p-Acylaminophenyl) imine of acetylacetone	6.9	2.58	15	80	1-(p-Acylaminophenyl)-2-methyl-3-acetyl-5-hydroxyindole (IX)

• 2-Methyl-3-acetyl-5-hydroxybenzofuran was identified by a mixed melting point test

•• The mixture of crystals was separated by fractional recrystallization from methanol.

••• The mixture of crystals was separated by fractional recrystallization from acetic acid.

•••• Found %: N 5.08, 5.04. Calculated %: N 4.75.

Yield, %	M. p.	Empirical formula	Found, %		Calculated, %	
				H	C	
39	232—233°• (from methanol)	$C_{11}H_{10}O_3$	—	—	—	—
Total yield••	220—221 (from methanol)	$C_{15}H_{17}O_4N$	65.16, 65.27	6.00, 6.27	65.44	6.22
42	232—233 • (from benzene)		—	—	—	—
Total yield•••	187—189° (from acetic acid)	$C_{13}H_{15}O_3N$	67.02, 67.22	6.59, 6.55	66.93	6.48
20	232—234 • (from methanol)		—	—	—	—
Total yield••	234—236 (from methanol)	$C_{18}H_{17}O_2N$	77.59, 77.52	6.12, 6.20	77.39	6.13
49	233—234 • (from methanol)		—	—	—	—
37	264—265 (from acetic acid)	$C_{18}H_{17}O_2N$	77.74, 77.54	6.31, 6.17	77.39	6.13
50	262—263 (from acetic acid)	$C_{18}H_{17}O_3N$	73.21, 72.93	5.74, **** 5.83	73.20	5.80
12	245—246 (from acetic acid)	$C_{18}H_{17}O_3N$	73.58, 73.42	5.76, 6.00	73.20	5.80
58	285—287 (from acetic acid)	$C_{19}H_{20}O_2N_2$	73.68, 73.69	6.47, 6.69	74.02	6.49
57	282—284 (from acetic acid)	$C_{19}H_{18}O_3N_2$	71.11, 71.03	5.37, 5.40	70.79	5.63

with a sample obtained previously [5].

TABLE 2

## Methylation of 5-Hydroxyindole Derivatives

Initial 5-hydroxyindoles com- pound	Initial amount, g	Dimethyl sulfate, cc	2 N Caustic soda, ml	Dioxan, ml	Indole derivatives obtained	Yield, %	M. p.	Empirical formula	Found, %		Calculated, %	
									C	H	C	H
II	1.36	1.27	5	4	Ethyl ester of (2-methyl-3-acetyl-5-methoxyindolyl-1)-acetic acid (X)	63	113–114° [from a benzene: petroleum ether mixture (1:2)]	$C_{18}H_{19}O_4N$	66.23, 66.39	6.78, 6.43	66.43	6.57
III	1.2	1.27	5	11	1-( $\beta$ -Methoxyethyl)-2-methyl-3-acetyl-5-methoxyindole (XI)	55	139–140 (from benzene)	$C_{15}H_{19}O_3N$	69.02, 68.75	7.11, 6.98	68.96	7.28
IV	5.58	5.08	20	16	1-Benzyl-2-methyl-3-acetyl-5-methoxyindole (XII)	86	99–100 (from petroleum ether)	$C_{19}H_{19}O_2N$	77.85, 77.94	6.39, 6.68	77.79	6.53
V	2.79	2.54	10	8	1-(p-Tolyl)-2-methyl-3-acetyl-5-methoxyindole (XIII)	92	169–170 (from methanol)	$C_{19}H_{19}O_2N$	78.03, 77.84	6.66, 6.41	77.79	6.53
VI	2.59	2.54	10	8	1-(p-Methoxyphenyl)-2-methyl-3-acetyl-5-methoxyindole (XIV)	97	235–237 (from acetic acid)	$C_{19}H_{19}O_3N$	73.41, 73.62	6.02, 6.03	73.76	6.19
VII	0.74	0.63	2.5	2	1-(o-Methoxyphenyl)-2-methyl-3-acetyl-5-methoxyindole (XV)	65	125–126 (from methanol)	$C_{19}H_{19}O_3N$	73.56, 73.50	6.37, 6.22	73.76	6.19
VIII	1.54	1.27	5	4	1-(p-Dimethylaminophenyl)-2-methyl-3-acetyl-5-methoxyindole (XVI)	94	207–208 (from dioxan)	$C_{20}H_{22}O_3N_2$	74.78, 74.63	7.11, 6.89	74.51	6.88
IX	3.2	2.54	10	8	1-(p-Acylaminophenyl)-2-methyl-3-acetyl-5-methoxyindole (XVII)	70	213–214 (from methanol)	$C_{20}H_{20}O_3N_2$	71.11, 71.44	6.14, 6.27	71.43	5.95



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# INVESTIGATIONS IN THE FIELD OF QUINONES

## XXXVII. CONDENSATION OF p-BENZOQUINONE WITH ANILIDES OF $\beta$ -AMINO-CROTONIC ACIDS

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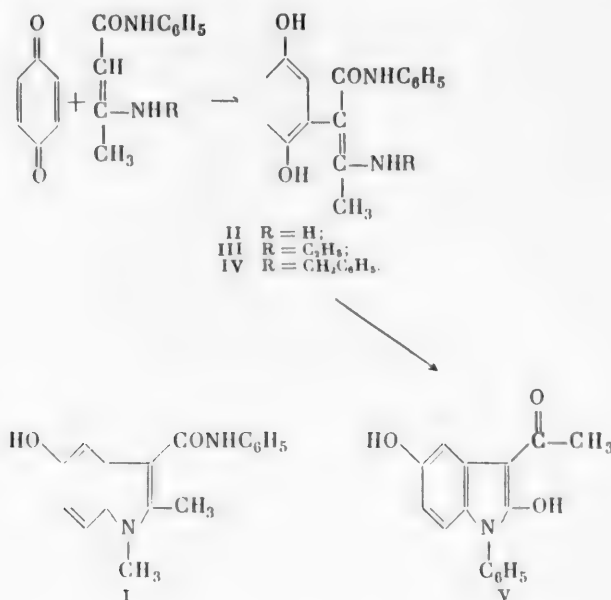
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 7,

pp. 2303-2306, July, 1961

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Anilides of  $\beta$ -aminocrotonic acid and N-alkyl- $\beta$ -aminocrotonic acids obtained by the method in [1,2] react with p-benzoquinone. The condensation was carried out by a method developed by the authors [3] from a study of a number of examples of the reaction of p-benzoquinone with esters of  $\beta$ -aminocrotonic acids.

When the anilide of N-methyl- $\beta$ -aminocrotonic acid reacted with p-benzoquinone we obtained the anilide of 1,2-dimethyl-5-hydroxyindolyl-3-carboxylic acid (I), whereas the condensation of p-benzoquinone with anilides of  $\beta$ -aminocrotonic, N-ethyl- $\beta$ -aminocrotonic and N-benzyl- $\beta$ -aminocrotonic acids leads to the formation of substituted hydroquinones (II-IV), which were previously considered intermediate reaction products.



When hydroquinones (II-IV) are heated in acetic acid in the presence of sulfuric acid they are converted to the 2,5-dihydroxyindole derivative (V), which, in contrast to 5-hydroxyindoles, gives a color with ferric chloride and forms a copper complex with copper acetate.

Methylation of the 5-hydroxyindole derivative (I) with dimethyl sulfate gives the anilide of 1,2-dimethyl-5-methoxyindolyl-3-carboxylic acid (VI), which when reduced by lithium aluminumhydride gives the hydrochloride of 1,2-dimethyl-3-anilinomethyl-5-methoxyindole (VII).

Initial Compounds	Quinone, g	Anilide, g	Dichloroethane, ml	Dichloroethane distilled as azeotropic mixture with water, ml in 15 min 1 hr	Substances obtained	Yield, %	M. p.	Empirical formula	Found, %		Calculated, %	
									C	H	C	H
p-Benzoquinone, anilide of $\beta$ -aminocrotonic acid	2	5.1	105	23	90	Anilide of $\alpha$ -(2', 5'-dihydroxyphenyl)- $\beta$ -aminocrotonic acid (II)	41	158° (from toluene)	C <sub>18</sub> H <sub>16</sub> O <sub>3</sub> N <sub>2</sub>	67.95, 5.90, 67.90, 6.00	67.59, 5.67	
p-Benzoquinone, anilide of $\beta$ -ethylaminocrotonic acid	6.7	19	215	30	150	Anilide of $\alpha$ -(2', 5'-dihydroxyphenyl)- $\beta$ -ethylaminocrotonic acid (III)	62	176—177° (from dioxan)	C <sub>19</sub> H <sub>20</sub> O <sub>3</sub> N <sub>2</sub>	68.89, 6.29, 69.01, 6.37	69.21, 6.45	
p-Benzoquinone, anilide of $\beta$ -benzylaminocrotonic acid	1	3.99	62	12	56	Anilide of $\alpha$ -(2', 5'-dihydroxyphenyl)- $\beta$ -benzylaminocrotonic acid (IV)	35	159—160° (from benzene)	C <sub>23</sub> H <sub>22</sub> O <sub>3</sub> N <sub>2</sub>	73.86, 5.96, 73.62, 6.00	73.78, 5.92	

## EXPERIMENTAL

### Anilide of N-ethyl- $\beta$ -aminocrotonic acid.

A solution of 9 g of ethylamine in 16 ml of anhydrous alcohol was added gradually to a solution of 20 g of the anilide of acetoacetic acid in 70 ml of anhydrous alcohol, heat being liberated by the reaction mixture. The solution obtained was left overnight at 0°. A third of the solvent was then distilled under vacuum. The residue was diluted with two volumes of water. Crystals formed from the oily layer. The crystals were filtered and dried in a vacuum desiccator over calcium chloride. The yield of the anilide was 22 g (92%); the m.p. was 88-89° (from petroleum ether).

Found %: C 70.86, 71.04; H 7.89, 7.97. C<sub>12</sub>H<sub>16</sub>ON<sub>2</sub>. Calculated %: C 70.79; H 7.84.

When the mixture obtained by the reaction of the anilide of acetoacetic acid with benzylamine was cooled, crystals of the anilide of N-benzyl- $\beta$ -aminocrotonic acid were formed. The yield was 73%; the m.p. was 86.5-87° (from alcohol).

Found %: C 76.32, 76.35; H 7.05, 6.86. C<sub>17</sub>H<sub>18</sub>ON<sub>2</sub>. Calculated %: C 76.66; H 6.81.

Anilide of 1,2-dimethyl-5-hydroxyindolyl-3-carboxylic acid (I). 12.4 g of the anilide of N-methyl- $\beta$ -aminocrotonic acid and 198 ml of dichloroethane were added in one operation to a solution of 4.6 g of p-benzoquinone in 46 ml of dichloroethane. The reaction mixture was heated in a Wurtz flask on a boiling water bath. 62 ml of an azeotropic mixture of dichloroethane and water distilled over in 15 minutes. 160 ml of liquid was distilled in 1 hour. The residue was cooled. The crystalline precipitate which formed was separated and washed with ether. The mother liquor was left overnight at room temperature to allow the solvent to evaporate, a further number of crystals being formed during this process. The yield was 7.5 g (64%); the m.p. was 165-165.5° (from dichloroethane).

Found %: N 10.26, 10.11. C<sub>17</sub>H<sub>16</sub>O<sub>3</sub>N<sub>2</sub>. Calculated %: N 9.99.

The condensation of other anilides of substituted  $\beta$ -aminocrotonic acids with p-benzoquinone was carried out in a similar way. The results obtained are given in the table.

Anilide of 1,2-dimethyl-5-methoxyindolyl-3-carboxylic acid (VI). Compound (I) was meth-

\* The synthesis of the anilides of  $\beta$ -aminocrotonic and N-methyl- $\beta$ -aminocrotonic acids was carried out according to literature data [1,2].

ylated under the conditions described in our previous article [1]. We took 6 g of compound (I), 5.3 g of dimethyl sulfate, 21.6 ml of 2 N caustic soda and 10 ml of dioxan. The 5-methoxyindole (VI) obtained was recrystallized from dioxan. The yield was 3 g (49%); the m.p. was 132-132.5°.

Found %: N 9.63, 9.68.  $C_{18}H_{18}O_2N_2$ . Calculated %: N 9.49.

Hydrochloride of 1,2-dimethyl-3-anilinomethyl-5-methoxyindole (VII). 2 g of compound (VI) was added gradually while stirring to a solution of 0.54 g of lithium aluminum hydride in 46 ml of anhydrous tetrahydrofuran. The reaction mixture was boiled for 4 hours in a flask with a reflux condenser and was left for a day at room temperature. The excess lithium aluminum hydride and the complex were decomposed by the gradual addition of 20 ml of water. The amine was extracted from the precipitate formed by means of ether. The ethereal extracts were dried by magnesium sulfate. A solution of 0.2 g of hydrogen chloride in absolute ether was added to an ethereal solution of the base (VII) while cooling and stirring. The amine chloride of (VII) separated out in the form of a viscous mass, which was crystallized by the addition of small quantities of water and alcohol. The crystals of (VII) chloride obtained were recrystallized from distilled water and dried in a vacuum desiccator, first over caustic soda and then over phosphorus pentoxide. The yield of (VII) chloride was 1.3 g (65%); the m.p. was 112-113°.

Found %: C 68.42, 68.51; H 6.48, 6.67.  $C_{18}H_{20}ON_2 \cdot HCl$ . Calculated %: C 68.30; H 6.63.

1-Phenyl-2,5-dihydroxy-3-acetylindole (V). One drop of concentrated sulfuric acid was added to a solution of 1 g of the anilide of  $\alpha$ -(2',5'-dihydroxyphenyl)- $\beta$ -aminocrotonic acid (II) in acetic acid, and the solution obtained was boiled for 1 hour in a flask with a reflux condenser. The crystals of (V) which separated when the reaction solution was cooled were filtered. A further quantity of (V) was obtained when water was added to the mother liquor. The yield was 0.6 g (73%); the m.p. was 235-236° (from methanol).

The 2,5-dihydroxyindole derivative (V) gave a positive reaction with ferric chloride and formed a complex with copper acetate.

Found %: C 71.56, 71.65; H 4.94, 5.04.  $C_{16}H_{13}O_3N$ . Calculated %: C 71.9; H 4.9.

The acetyl derivative obtained by heating the 2,5-dihydroxyindole (V) with acetic anhydride had a m.p. of 149-150°.

Cyclization of other substituted hydroquinones (III, IV) to the 2,5-dihydroxyindole (V) was carried out similarly.

#### SUMMARY

1. The anilide of 1,2-dimethyl-5-hydroxyindolyl-3-carboxylic acid was obtained by condensation of the anilide of N-methyl- $\beta$ -aminocrotonic acid with p-benzoquinone.

2. The reaction of p-benzoquinone with anilides of other  $\beta$ -aminocrotonic acids leads to the formation of substituted hydroquinones, which were previously considered intermediate products of the reaction.

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## INVESTIGATION OF PYRAZOLES

### XIX. AMINOPYRAZOLES AS AMINO COMPONENTS IN SKRAUP'S SYNTHESIS.

#### SYNTHESIS OF PYRAZOLOPYRIDINES

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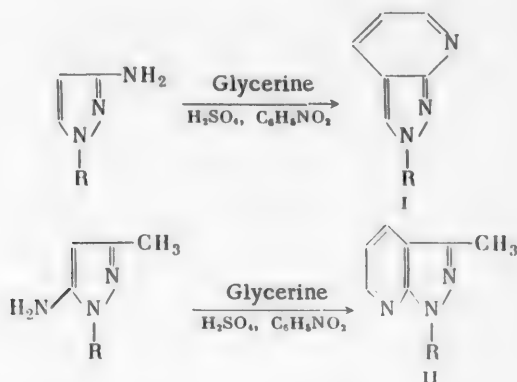
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 7,

pp. 2307-2310, July, 1961

Original article submitted July 4, 1960

In 1958 it was shown that 1-phenyl-4-aminopyrazole takes part in Skraup's synthesis, giving a pyrazolopyridine of unknown structure. 3-Methyl-1-phenyl-4-amino- and 5-methyl-1-phenyl-4-aminopyrazoles took part in this condensation, but the pyrazolopyridines obtained had a well-defined structure; however, in both cases the yields were low [1]. With an amino group present in the 4 position of the pyrazole ring, condensation must take place by means of the hydrogen atom in the 3 or 5 position of the ring, but, as is well known, these positions of the ring hardly ever show aromatic properties.

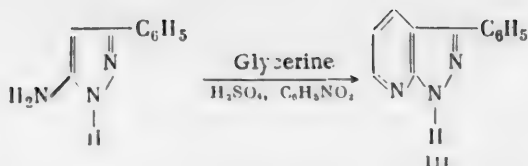
At the same time, if the amino group is in the 3 or 5 position, the 4 hydrogen atom, which is extremely active in many reactions, must take part in the condensation. As we expected, 5- and 3-aminopyrazoles substituted at the nitrogen atom of the ring took part in Skraup's synthesis, giving pyrazolo (4': 5'-2: 3) pyridines (II) and pyrazolo (3': 4'-2: 3) pyridines (I), respectively, in 30-60% yields.



All the aminopyrazoles were reacted under standard conditions. 1-Phenyl-3-aminopyrazole gave pyrazolopyridine (I) with hardly any mixture of the initial amine; however, 5-aminopyrazoles formed pyrazolopyridines (II) markedly contaminated by the initial amine. Since purification by distillation was ineffective because of the similar boiling points, we employed toluene sulfonyl chloride for purification, with good results.

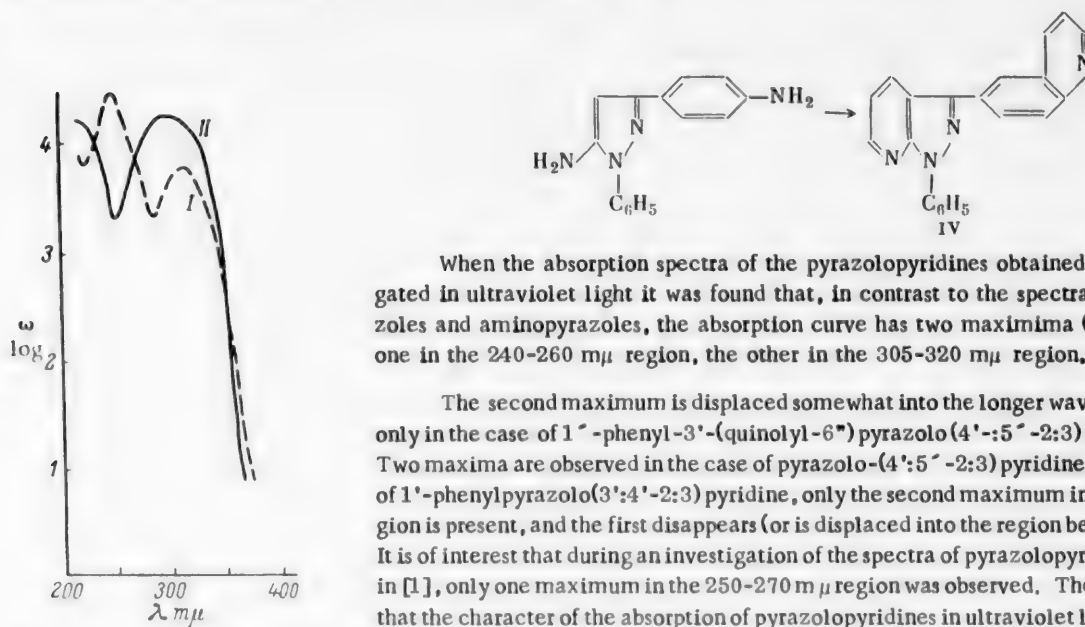
1-Phenyl-3-aminopyrazole was synthesized by the method we described in [2]. 5-Aminopyrazoles were obtained by condensation of diacetonitrile with the corresponding hydrazines [3].

The behavior of 3-phenyl-5-aminopyrazole, 3-(p-aminophenyl)-5-aminopyrazole and 1-phenyl-3-(p-aminophenyl)-5-aminopyrazole in Skraup's synthesis was of particular interest. In the first two cases the free NH group of pyrazole may obstruct the reaction.



In fact, although in the case of 3-phenyl-5-aminopyrazole we obtained the desired pyrazolopyridine (III), the yield was only 14%. But in the case of 3-(p-aminophenyl)-5-aminopyrazole we did not succeed in obtaining the individual compounds at all.

However, if the hydrogen of the amino group is replaced by any radical [for instance, if 1-phenyl-3-(p-aminophenyl)-5-aminopyrazole is introduced into the reaction] the yield of pyrazolopyridine (IV) is at once increased to 60%, the Skraup synthesis taking place at both amino groups.



When the absorption spectra of the pyrazolopyridines obtained were investigated in ultraviolet light it was found that, in contrast to the spectra of the pyrazoles and aminopyrazoles, the absorption curve has two maxima (see figure), one in the 240-260 mμ region, the other in the 305-320 mμ region.

The second maximum is displaced somewhat into the longer wave region (337 mμ) only in the case of 1'-phenyl-3'-(quinolyl-6'') pyrazolo(4':5'-2:3) pyridine (IV). Two maxima are observed in the case of pyrazolo-(4':5'-2:3) pyridines. But in the case of 1'-phenylpyrazolo(3':4'-2:3) pyridine, only the second maximum in the 307 mμ region is present, and the first disappears (or is displaced into the region below 220 mμ). It is of interest that during an investigation of the spectra of pyrazolopyridines obtained in [1], only one maximum in the 250-270 mμ region was observed. Therefore, it follows that the character of the absorption of pyrazolopyridines in ultraviolet light depends fundamentally on the form of the bond of the pyrazole and pyridine nuclei.

Ultraviolet spectra of pyrazolopyridines (solvent—methanol, SF-4).

I) 1'-Phenylpyrazolo(4':5'-2:3) pyridines; II) 1'-phenylpyrazolo-(3':4'-2:3) pyridines (see table).

ring vigorously. A further 60 ml of concentrated hydrochloric acid was added and the mixture was heated to boiling. After it had cooled, the reaction mass was made alkaline with excess caustic soda and the liberated oil was extracted with benzene. By distillation of the benzene extract we obtained 60.5 g (81%) of aminopyrazole with a b.p. of 187-192° (8 mm), m.p. 69-70° (from petroleum ether).

Found %: C 70.99, 70.93; H 7.27, 7.11.  $C_{11}H_{13}N_3$ . Calculated %: C 70.77; H 7.00.

The m.p. of the picrate was 145-146° (from methanol).

Found %: N 20.03, 20.00.  $C_{11}H_{13}N_3 \cdot C_6H_5O_7N_3$ . Calculated %: N 20.12.

1-(β-Phenethyl)-3-methyl-5-aminopyrazole. This compound was obtained by a similar method from 0.4 mole of β-phenethylhydrazine, with a yield of 80%; the b.p. was 184-189° (6 mm); the m.p. was 108.5-109.5 (from benzene).

Found %: N 21.07, 21.03.  $C_{12}H_{15}N_3$ . Calculated %: N 20.87.

The m.p. of the picrate was 180-180.5° (from methanol).

#### EXPERIMENTAL

1-Benzyl-3-methyl-5-aminopyrazole. 48.8 g of benzylhydrazine was dissolved in a mixture of 45 ml of concentrated hydrochloric acid and 150 ml of water, and 30.2 g of diacetonitrile was added slowly at 60° to the mixture while stirring vigorously.



Found %: N 19.86, 19.64.  $C_{12}H_{15}N_3 \cdot C_6H_5O_7N_3$ . Calculated %: N 19.53.

Compound	log $\epsilon$	$\lambda_{max}$ , m $\mu$
1'-Phenylpyrazolo (3': 4'-2: 3) pyridine	4.22	307
1'-Phenyl-3'-methylpyrazolo (4: 5'-2: 3) pyridine	4.43, 3.72	252, 317
1'-( $\beta$ -Phenethyl)-3'-methylpyrazolo (4': 5'-2: 3) pyridine	3.47, 3.56	265, 312
1'-Phenyl-3'-(quinolyl-6'') pyrazolo (4': 5'-2: 3) pyridine	4.64, 4.25	247, 337
3'-Phenylpyrazolo (4': 5'-2: 3) pyridine	4.21, 3.93	242, 312
1'-Phenylpyrazolo (4': 5'-2: 3) pyridine	4.44, 3.57	252, 307

1'-Phenylpyrazolo (3': 4'-2: 3) pyridine. 31.3 g of 1-phenyl-3-aminopyrazolo [2], 45.2 g of sulfuric acid (d 1.86), 84.6 g of anhydrous glycerine and 17.8 g of nitrobenzene were mixed in a 500 ml flask equipped with a large Dimroth reflux condenser. The reaction mixture was heated slowly. Reaction commenced at 130° (in the mixture) and proceeded fairly smoothly. The reaction mixture was boiled for 6 hours at 130-140° (in the mixture). The nitrobenzene was then steam distilled from the reaction mixture; the residue in the flask was made alkaline with excess 40% caustic soda and was extracted repeatedly with boiling benzene. The benzene extracts were distilled under vacuum in a flask with a sword-type adapter. We obtained 19.3 g (46.5%) of crude 1'-phenylpyrazolo(3':4'-2:3)pyridine with a b.p. of 180-205° (1 mm); the m.p. was 118-119° (from benzene).

To remove final traces of the initial amine (which had a similar boiling point) and other impurities, this compound and all the other pyrazolopyridines were purified as follows. 0.1 g-mole of pyrazolopyridine was dissolved in 15 ml of anhydrous pyridine and was left to stand overnight after 0.1 g-mole of p-toluene sulfonyl chloride had been added. 100 ml of 2 N caustic soda was added to the reaction mixture, which was boiled for 10 minutes. The pure pyrazolopyridine obtained was extracted with benzene and distilled under vacuum. The boiling point of the pure compound was 189-190° (1 mm); the m.p. was 119-120° (from benzene).

Found %: C 74.24, 74.18; H 4.94, 4.84; N 21.89, 21.86.  $C_{12}H_9N_3$ . Calculated %: C 73.87; H 4.64; N 21.52.

The m.p. of the picrate was 216° (from a large quantity of alcohol).

Found %: C 50.66, 50.62; H 3.00, 2.96; N 19.79, 19.75.  $C_{12}H_9N_3 \cdot C_6H_5O_7N_3$ . Calculated %: C 50.92; H 2.85; N 19.79.

1'-Phenyl-3'-methylpyrazolo (4': 5'-2: 3') pyridine was obtained by a similar method from 0.2 g-mole of 1-phenyl-3-methyl-5-aminopyrazole [3], the yield being 31.4%; the b.p. was 167-169° (2 mm); the m.p. was 54° (from petroleum ether).

Found %: C 74.52, 74.45; H 5.39, 5.36.  $C_{13}H_{11}N_3$ . Calculated %: C 74.63; H 5.30.

The m.p. of the picrate was 71-71.5° (from methanol).

Found %: N 19.29, 19.28.  $C_{13}H_{11}N_3 \cdot C_6H_5O_7N_3$ . Calculated %: N 19.18.

1'-Benzyl-3'-methylpyrazolo (4': 5'-2: 3) pyridine was obtained by a similar method from 0.2 g-mole of 1-benzyl-3-methyl-5-aminopyrazolo, the yield being 46.8%; the b.p. was 153-155° (2 mm); the m.p. was 46-47° (from petroleum ether).

Found %: C 64.93, 64.71; H 6.64, 6.42; N 18.96, 18.76.  $C_{14}H_{13}N_3$ . Calculated %: C 64.83; H 6.44; N 18.90.

The m.p. of the picrate was 163-163.5° (from methanol).

Found %: N 18.68, 18.60.  $C_{14}H_{13}N_3 \cdot C_6H_5O_7N_3$ . Calculated %: N 18.62.

1'-Phenylpyrazolo (4': 5'-2: 3) pyridine was obtained by a similar method from 0.2 g-mole of 1-phenyl-5-aminopyrazole [4], with a yield of 34.2%. The b.p. was 155-157° (3 mm); the m.p. was 53.5-54° (from petroleum ether).

Found %: C 73.52, 73.36; H 5.03, 5.00; N 21.42, 21.21.  $C_{12}H_9N_3$ . Calculated %: C 73.87; H 4.64; N 21.52.

The m.p. of the picrate was 95-97° (from methanol).

Found %: N 20.25, 20.15.  $C_{12}H_9N_3 \cdot C_6H_5O_7N_3$ . Calculated %: N 19.79.

1'-( $\beta$ -Phenethyl)-3'-methylpyrazolo (4': 5'-2: 3) pyridine was obtained by a similar method from 0.2 g-mole of 1- $\beta$ -phenethyl-3-methyl-5-aminopyrazole, the yield being 37.6%; the b.p. was 161-163° (2 mm); the m.p. was 32-33.5° (from petroleum ether).

Found %: C 75.92, 75.81; H 6.24, 6.18; N 18.05, 17.98.  $C_{15}H_{15}N_3$ . Calculated %: C 76.23; H 5.98; N 17.79.

The m.p. of the picrate was 132° (from methanol).

Found %: N 18.45, 18.32.  $C_{15}H_{15}N_3 \cdot C_6H_3O_7N_3$ . Calculated %: N 18.07.

3-Phenylpyrazolo (4': 5'-2: 3) pyridine was obtained by a similar method, without purification by sulfonyl chloride, from 0.1 g-mole of 3-phenyl-5-aminopyrazole [3]. The yield was 14%, the b.p. was 203-207° (3 mm) and the m.p. was 168-169° (from benzene-petroleum ether).

Found %: C 73.83, 73.74; H 5.09, 5.07.  $C_{12}H_9N_3$ . Calculated %: C 73.87; H 4.64.

The m.p. of the picrate was 229-232° (from methanol).

Found %: N 19.91, 19.82.  $C_{12}H_9N_3 \cdot C_6H_3O_7N_3$ . Calculated %: N 19.79.

1'-Phenyl-3'-(quinolyl-6'') pyrazolo (4': 5'-2: 3) pyridine was obtained in a similar way, without purification by sulfonyl chloride, from 0.1 g-mole of 1-phenyl-3-p-aminophenyl-5-aminopyrazole [3], with a yield of 58%; the b.p. was 282-286° (3 mm); the m.p. was 147.5-148° (from benzene).

Found %: C 78.00, 77.81; H 4.68, 4.61.  $C_{20}H_{14}N_4$ . Calculated %: C 78.25; H 4.38.

The m.p. of the dipicrate was 252-235° (from methanol).

Found %: N 18.19, 18.15.  $C_{20}H_{14}N_4 \cdot 2C_6H_3O_7N_3$ . Calculated %: N 17.96.

#### SUMMARY

1. It is shown that aminopyrazoles with the amino group in the 3 or 5 position of the ring take part in the Skraup synthesis in a similar way to aromatic amines.

2. As a result of the reaction, pyrazolopyridines, new compounds of a class which has been little investigated, were obtained.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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## INVESTIGATION OF PYRAZOLES

### XX. SYNTHESIS OF 5-AMINOPYRAZOLES AND THEIR SULFONAMIDE DERIVATIVES

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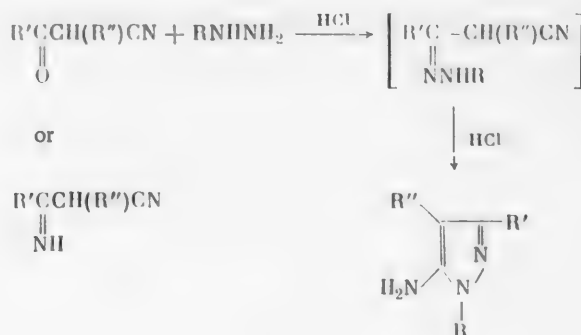
Translated from Zhurnal Obshchei Khimii, Vol.31, No. 7,

pp. 2311-2315, July, 1961

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A new effective sulfonamide, "orisul," a derivative of 1-phenyl-5-aminopyrazole, was recently patented [1]. We synthesized a number of similar compounds with the aim of assessing their antibacterial activity.

The most convenient method of obtaining 5-aminopyrazoles is the reaction of  $\beta$ -ketonitriles or their derivatives with hydrazines [2].



All the 5-aminopyrazoles we obtained were synthesized by this method with high yields (Table 1). The yields were less than 30-40% only in the case of ortho-substituted aryl hydrazines. The reaction was carried out in hydrochloric acid, the hydrazones formed being converted at once, without separation, to aminopyrazoles by adding a large amount of concentrated hydrochloric acid. 5-Aminopyrazoles unsubstituted at the nitrogen of the heterocyclic ring were obtained by reacting  $\beta$ -ketonitriles with hydrazine hydrate [3].

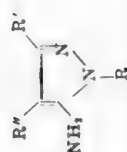
We synthesized the initial  $\beta$ -ketonitriles by condensation of the corresponding nitriles by means of sodium metal [4]. We obtained  $\omega$ -cyanoacetophenones by the reaction of substituted benzoyl chlorides with cyanoacetic ester [5].

5-p-Aminophenylsulfamidopyrazoles were synthesized by reacting 5-aminopyrazoles with p-acetaminobenzenesulfonyl chloride in anhydrous pyridine [6].

In the case of the sulfonamide derivative of 1-p-nitrophenyl-3-methyl-5-aminopyrazole, we did not succeed in hydrolyzing the acetyl group. During this process the labile sulfonamide bond is evidently broken, due to the very low basicity of the amino group of pyrazole; as a result of hydrolysis the initial aminopyrazole is re-obtained.

Replacement of the hydrogen atom in the 5 position of the ring by an amino group hardly changes the character of the curve of the UV spectrum of the initial pyrazole and does not displace the maximum (figure). All alkyl derivatives of 5-aminopyrazoles have a weakly expressed maximum in the 215-225 m $\mu$  region, a general characteristic of pyrazoles with alkyl substituents. Irrespective of the position of the aryl group, aryl derivatives have a maximum in the 245-285 m $\mu$  region, which also agrees with data for aryl pyrazoles [7].

TABLE 1 1-Substituted 3-Alkyl-5-aminopyrazoles



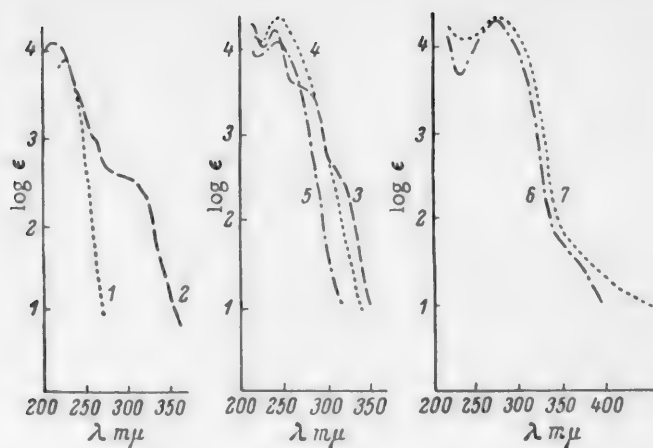
R	R'	R	Yield, %	M. p.	B. p. (pressure in mm)	Empirical formula	% N	
							found	calculated
C <sub>6</sub> H <sub>5</sub> C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>	CH <sub>3</sub>	H	81	110–111° [2]	158–193° (8) 180–187° (5)	C <sub>10</sub> H <sub>11</sub> N <sub>3</sub> C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> C <sub>13</sub> H <sub>15</sub> N <sub>3</sub>	18.83, 30.42,	18.83 30.22
			78	69–71 [7]				
			76	108–109 [8]				
β-C <sub>10</sub> H <sub>7</sub> iso-C <sub>10</sub> H <sub>7</sub> o-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	H	76	149–150	131–132 (21)	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> C <sub>7</sub> H <sub>13</sub> N <sub>3</sub> C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> **	20.97, 16.61, 25.35,	20.87 16.73 25.15
			70	111–112				
			35.5	87 [9]				
C <sub>6</sub> H <sub>5</sub> β-C <sub>10</sub> H <sub>7</sub> iso-C <sub>10</sub> H <sub>7</sub> o-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	82	60–61	137–138 (19) 174–176° (8)	C <sub>12</sub> H <sub>15</sub> N <sub>3</sub> *** C <sub>10</sub> H <sub>17</sub> N <sub>3</sub> C <sub>9</sub> H <sub>17</sub> N <sub>3</sub>	20.97, 16.61, 25.35,	20.87 16.73 25.15
			72	85–86				
			65	62–63				
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	H	36	57–58		C <sub>13</sub> H <sub>17</sub> N <sub>3</sub>	19.67,	19.60
			90	161–162				
						C <sub>10</sub> H <sub>10</sub> O <sub>2</sub> N <sub>4</sub> ****	25.70,	25.69

\* Picrate, m.p. 153°.

\*\* Picrate, m.p. 181°. Found %: N 20.05, 19.78. C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>·C<sub>6</sub>H<sub>5</sub>O<sub>7</sub>N<sub>3</sub>. Calculated %: N 20.02.

\*\*\* According to [10], the m.p. is 81°.

\*\*\*\* By nitration of 1-phenyl-3-methyl-5-aminopyrazole, Michaelis [11] obtained a substance with a m.p. of 98–99°, which he described as 1-(p-nitrophenyl)-3-methyl-5-aminopyrazole. The substance we obtained gives a picrate with a m.p. of 156–157°; it is not a hydrazone. In Michaelis' investigations, partial nitration in the 4 position of the pyrazole ring evidently occurred, and he obtained a mixture of compounds.



Ultraviolet absorption curves of 5-aminopyrazoles (SF-4, solvent—methanol).

1) 1-Isopropyl-3-methyl-5-aminopyrazole,  $\lambda_{\max}$  228,  $\log \epsilon$  3.86; 2) 1-benzoyl-3-methyl-5-aminopyrazole,  $\lambda_{\max}$  220,  $\log \epsilon$  4.00; 3) 1-naphthyl-3-methyl-5-aminopyrazole,  $\lambda_{\max}$  250,  $\log \epsilon$  4.20; 4) 3-phenyl-5-aminopyrazole,  $\lambda_{\max}$  247,  $\log \epsilon$  4.33; 5) 1-phenyl-3-ethyl-4-methyl-5-aminopyrazole,  $\lambda_{\max}$  250,  $\log \epsilon$  4.09; 6) 3-p-aminophenyl-5-aminopyrazole,  $\lambda_{\max}$  277,  $\log \epsilon$  4.34; 7) 1-phenyl-3-p-aminophenyl-5-aminopyrazole,  $\lambda_{\max}$  282,  $\log \epsilon$  4.37.

#### EXPERIMENTAL

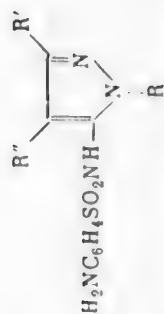
**1-Substituted 3-alkyl-5-aminopyrazoles (Table 1).** 1 g-mole of hydrazine was dissolved in 100 ml of concentrated hydrochloric acid and 400 ml of water in a beaker. 1 g-mole of  $\beta$ -ketonitrile (diacetonitrile or 2-methyl-3-ketiminovalelonitrile [4]) was then added to the solution while stirring vigorously; stirring was continued for 10 minutes. A further 200 ml of concentrated hydrochloric acid was added to the reaction mixture, which was then boiled for 15 minutes. It was cooled, made alkaline with dilute ammonia (in the case of aminopyrazoles difficultly soluble in water) or with a large excess of solid caustic soda (in the case of aminopyrazoles with a low molecular weight, up to  $C_{10}$ ). The aminopyrazole was separated, dried and purified by recrystallization from a mixture of benzene and petroleum ether. When large amounts were synthesized, it was preferable to purify the aminopyrazole by distillation.

TABLE 2 3-Aryl-5-aminopyrazoles

$  \begin{array}{c}  \text{H}_2\text{N} \\  \diagup \quad \diagdown \\  \text{N} \quad \text{N} \\  \diagdown \quad \diagup \\  \text{N} \\    \\  \text{R}  \end{array}  \quad \text{R}'  $				
R	R'	Yield%	M.p.	Empirical formula
$C_6H_5$	H	60	123° [12]	$C_{15}H_{13}N_3$
$C_6H_5$	$NH_2$	82	110 [13]	$C_{13}H_{14}N_4$
$C_6H_5$	$OC(=O)CH_3$	80	186—187 [14]	$C_{16}H_{15}ON_3$
H	H	55	121—126 [3]	$C_8H_6N_3$
H	$NH_2$	89	210—211*	$C_9H_{10}N_4$

\*Found %: N 32.29, 32.51. Calculated %: N 32.18.

TABLE 3. Sulfonamide Derivatives of 5-Aminopyrazoles



R	R'	R	Yield, %	M. p.	Empirical formula	% N	
						found	calculated
$\text{C}_6\text{H}_5$			65	181–182° [14]	$\text{C}_{16}\text{H}_{16}\text{O}_2\text{N}_4\text{S}$	17.25, 17.19	17.38
<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4$			66	188–189	$\text{C}_{17}\text{H}_{18}\text{O}_2\text{N}_4\text{S}$	16.11, 16.35	16.37
<i>p</i> - $\text{C}_{10}\text{H}_7$			70	185–186	$\text{C}_{20}\text{H}_{16}\text{O}_2\text{N}_4\text{S}$	14.49, 14.58	14.82
$\text{C}_6\text{H}_5\text{CH}_2$	$\text{CH}_3$	H	81	219–220 (decom.)	$\text{C}_{17}\text{H}_{18}\text{O}_2\text{N}_4\text{S}$	16.51, 16.68	16.37
$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2$			82	210–211 (decom.)	$\text{C}_{18}\text{H}_{20}\text{O}_2\text{N}_4\text{S}$	15.90, 16.10	15.73
iso- $\text{C}_3\text{H}_7$	$\text{CH}_3$	H	42	177–178	$\text{C}_{13}\text{H}_{18}\text{O}_2\text{N}_4\text{S}$	19.71, 19.61	19.07
$\text{C}_6\text{H}_5$			67	200–201	$\text{C}_{18}\text{H}_{20}\text{O}_2\text{N}_4\text{S}$	15.63, 15.45	15.73
<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4$			62	118–119	$\text{C}_{19}\text{H}_{22}\text{O}_2\text{N}_4\text{S}$	15.14, 15.24	15.01
<i>p</i> - $\text{C}_{10}\text{H}_7$	$\text{C}_2\text{H}_5$	$\text{CH}_3$	69	224–225	$\text{C}_{22}\text{H}_{22}\text{O}_2\text{N}_4\text{S}$	13.80, 13.75	13.79
iso- $\text{C}_3\text{H}_7$			47	174–175	$\text{C}_{15}\text{H}_{22}\text{O}_2\text{N}_4\text{S}$	17.72, 17.46	17.40
H	$\text{C}_6\text{H}_5$	H	60	253–254	$\text{C}_{15}\text{H}_{14}\text{O}_2\text{N}_4\text{S}$	17.92, 17.68	17.83
$\text{C}_6\text{H}_5$	<i>p</i> - $\text{CH}_2\text{OC}_6\text{H}_4$	H	67	232	$\text{C}_{22}\text{H}_{20}\text{O}_3\text{N}_4\text{S}$	13.55, 13.50	13.33
$\text{C}_6\text{H}_5$	<i>p</i> - $\text{NH}_2\text{C}_6\text{H}_4\text{SO}_2\text{HNC}_6\text{H}_4$	H	42	Decomposition above 180°	$\text{C}_{27}\text{H}_{24}\text{O}_4\text{N}_6\text{S}_2$	14.40, 14.25	15.00
$\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5$	H	69	229	$\text{C}_{21}\text{H}_{18}\text{O}_2\text{N}_4\text{S}$	14.30, 14.17	14.36



3-Aryl-5-aminopyrazoles (Table 2). 1-Phenyl-3-aryl-5-aminopyrazoles (the first three compounds in Table 2) were obtained from phenylhydrazine and the corresponding substituted  $\omega$ -cyanoacetophenone by the above-described method. To obtain 3-aryl-5-aminopyrazoles unsubstituted at the nitrogen, we placed 0.1 g-mole of  $\omega$ -cyanoacetophenone [5], 100 ml of alcohol and 0.2 g-mole of 96% hydrazine hydrate in a round-bottomed flask equipped with a reflux condenser. The reaction mixture was heated on a boiling water bath for 8 hours. The residue generally crystallized on standing; it was recrystallized from ethyl acetate or petroleum ether with benzene.

Sulfonamide derivatives of 5-aminopyrazoles (Table 3). 0.125 g-mole (0.25 g-mole in the case of 3-p-aminophenyl-5-aminopyrazoles) of p-acetamino-benzenesulfonyl chloride was added slowly in portions with vigorous stirring to a mixture of 0.1 g-mole of 5-aminopyrazole and 12 ml of anhydrous pyridine. The reaction was exothermic. The mixture was left at room temperature for 24 hours. p-acetaminophenylsulfamido-5-aminopyrazole was precipitated by adding 100 ml of cold water and 10 ml of concentrated hydrochloric acid. The acetyl derivative was hydrolyzed by boiling for 3 hours with 100 ml of 15% caustic soda. After it had cooled, the reaction mixture was filtered through an 8 mm layer of activated carbon and the filtrate was acidified with dilute hydrochloric acid. The precipitate was filtered, washed with cold water and recrystallized from dilute alcohol and a petroleum ether-benzene mixture.

#### SUMMARY

A number of 5-aminopyrazoles were obtained and were used for the synthesis of sulfonamide derivatives, which are potential antimicrobial agents.

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## COMPLEX-FORMING SUBSTANCES

### VL SYNTHESIS OF CYCLIC ANALOGS OF CYANOTRIACETIC AND ETHYLENEDIAMINETETRAACETIC ACIDS

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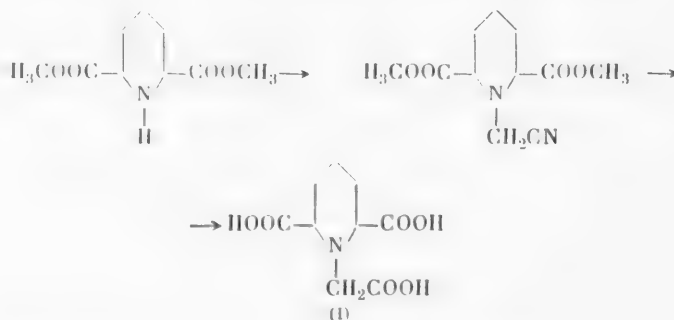
With the aim of finding efficient complex-formers, a large number of derivatives and analogs of cyanotriacetic (CTA) and ethylenediaminetetraacetic (EDTA) acids, the most widely used complexons, have now been synthesized and investigated.

Of a great many compounds of this type, only 1,2-diaminecyclohexanetetraacetic [1] and 1,2-diaminecyclopentanetetraacetic [2,3] acids were found to have a higher complexing capacity than EDTA. In our opinion [3], this is due to stereochemical factors which are caused by the essential restricted rotation of the vicinal substituents in the cyclohexane and, in particular, the cyclopentane rings with respect to the C-C bond of the ring, which leads to a specific configuration of the aminodiacetic groups in the molecules of both complexes.

We considered it of interest to investigate the influence of the configuration of the carboxyl groups of aminodiacetic groups in the molecules of complexons (where this may occur) on the complexing capacity.

For this it was necessary to synthesize compounds in which a certain proportion, at least, of the carboxyl groups forming part of the aminodiacetic acid group was present in a fixed position. In this connection, for a comparison of the complexing properties it was desirable to have analogs or homologs of known complexons, in particular of CTA and EDTA.

In our opinion, 1-carboxymethylpiperidine-2,6-dicarboxylic (I) and 1,4-di(carboxymethyl)-piperazine-2,3-dicarboxylic (II) acids meet these requirements. Their synthesis is described in this report.



1-Carboxymethylpiperidine-2,6-dicarboxylic acid was obtained from 2,6-lutidine by oxidation to lutidinic acid, followed by esterification and hydrogenation of the pyridine ring. From the dimethyl ester of piperidine 2,6-dicarboxylic acid [4] we synthesized, by the cyanomethylation reaction, the dimethyl ester of 1-cyanomethylpiperidine, 2,6-dicarboxylic acid, which was converted to the acid (I) by saponification with alkali. The complexon obtained is a fine-crystalline colorless powder with a bluish tint; it is not readily soluble in water.

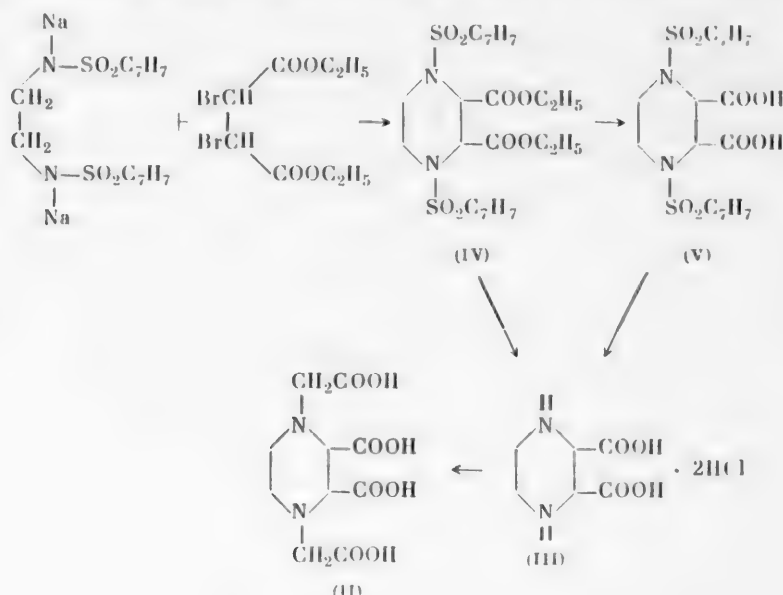
To obtain a cyclic analog of EDTA acid it was necessary to synthesize piperazine 2,3-dicarboxylic acid (III). We had to reject our original plan to reduce the relatively easily obtainable pyrazine dicarboxylic acid or its esters,

which was apparently the simplest method, because it was recently found [5] that esters of pyrazine dicarboxylic acids cannot in fact be converted to the corresponding hexahydro derivatives by hydrogenation.

We obtained acid (III) by a method similar to that described for the synthesis of piperazine monocarboxylic acid [6].

The disodium derivative of *N,N'*-di(*p*-toluene sulfonyl) ethylenediamine was condensed with the diethyl ester of 1,2-dibromosuccinic acid in the presence of alcoholic alkali. When the diethyl ester of *N,N'*-di(*p*-toluene sulfonyl) piperazine 2,3-dicarboxylic acid (IV) obtained was boiled with 48% hydrobromic acid, it did not lose the toluene sulfonyl group, as in the case of the monocarboxylic acid [6], but was converted to the corresponding dicarboxylic acid (V). Nor did saponification with concentrated hydrochloric acid at 130° in a sealed tube lead to removal of the sulfonic acid groups from the nitrogen atom. Conversion of the ester (IV) to the dihydrochloride of piperazine 2,3-dicarboxylic acid (III) was only obtained by heating with a mixture of 37% hydrochloric and glacial acetic acid (2:1) at 130-140° in a sealed tube. By reacting the dihydrochloride of acid (III) with excess monobromoacetic acid in the presence of caustic soda at 40° we synthesized complexon (II), precipitated by acidification of the reaction mass in the form of a fine crystalline colorless powder which was recrystallized from water.

The presence of asymmetric carbon atoms in the molecules of our synthesized complexons was associated with the existence of geometric and optical isomerism in the complexons and some of their parent compounds. It may be assumed that *trans*-isomers of piperidine and piperazine dicarboxylic acids must exist in the form of optically resolvable racemates, while the corresponding *cis*-isomers, having a plane of symmetry, would be irresolvable meso-forms.

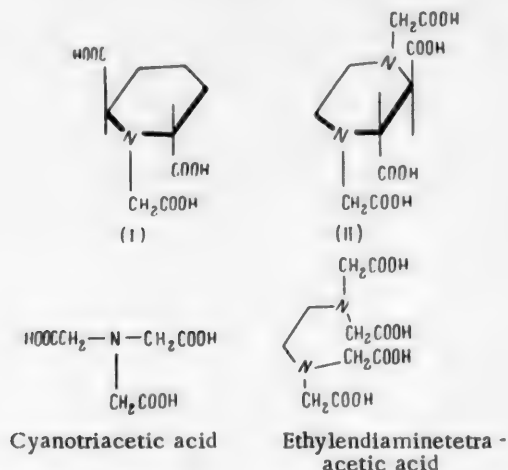


On the basis of experimental and literature data it may be assumed that our complexons (I) and (II) have a *trans*-configuration.

The dimethyl ester of piperidine-2,6-dicarboxylic acid obtained from 2,6-lutidine has a *cis*-configuration; however, as was expected [4], this ester and its *N*-methyl derivative are isomerized to the *trans*-form in alkali, this process taking place spontaneously when these substances are left standing without addition of any agent. In our case, during the cyanomethylation reaction the configuration of the diester molecule is evidently retained, but subsequent saponification of the cyanodiester by alkali under severe conditions undoubtedly leads to complete isomerization and the formation of *trans*-1-carboxymethylpiperidine-2,6-dicarboxylic acid.

The assumption that tetra acid (II) has a *trans*-configuration is based on the fact that as a result of condensation of the disodium derivative of *N,N'*-di(*p*-toluene sulfonyl) ethylenediamine with either racemic (from fumaric acid) or meso (from maleic acid) diethyl esters of dibromosuccinic acid we obtained the same diethyl ester (IV). Under

the conditions of the cyclization reaction, which is performed in boiling alcoholic potash, the *cis*-form of ester (IV) formed from one of the dibromosuccinic esters is evidently converted completely to the more stable *trans*-isomer, and the result of the conversion of both dibromosuccinic esters is the *trans*-form of ester (IV).



Examples of such isomerization are described in the literature. It is of interest to note that isomerization does not take place if the substituents in the piperazine ring are not of a complex-ester character, but methyl groups, for example. It was recently shown [7] that two isomeric 2,3-dimethyl piperazines are formed as a result of condensation of the disodium derivative of *N,N'*-di(*p*-toluene sulfonyl) meso and racemic 1,2-dimethyl ethylenediamine with dibromoethane under similar conditions.

During acid hydrolysis of ester (IV) and, furthermore, during condensation of the dihydrochloride of acid (III) with bromoacetic acid in the presence of alkali, it would be natural to expect retention of the *trans*-configuration and the formation of *trans*-1,4-di(carboxymethyl)-piperazine 2,3-dicarboxylic acid.

To confirm this assumption, we resolved optically one of the parent substances of complexon (II), i.e., acid (V). A solution of this compound in methanol was treated with a methanolic solution of the base cinchonine, the difficultly soluble dicinchoninic salt of one of the isomers of acid (V) being precipitated during this process. After treatment of this salt with hydrochloric acid the optically active acid (V) was isolated. Isolation of the other isomer, the cinchoninic salt of which was readily soluble in methanol, was unnecessary.

Therefore, we have shown that acid (V) and, in consequence, acid (III) and complexon (II) have a *trans*-configuration.

The results of work with the aim of obtaining *cis*-isomers of the synthesized complexons and investigating the complexing properties of the new complex-formers will be the subject of subsequent communications.

#### EXPERIMENTAL

Dimethyl ester of 1-cyanomethylpiperidine-2,6-dicarboxylic acid. 9 ml of 10% hydrochloric acid, 2.5 ml of 37% formalin and a solution of 1.5 g of sodium cyanide in 3 ml of water were added to 5 g of the dimethyl ester of piperidine-2,6-dicarboxylic acid (m.p. 90-91°) while stirring and cooling. The temperature of the reaction mixture did not exceed 15°. The mixture was stirred for 3 hours at this temperature and was left overnight at room temperature. The precipitate was filtered and washed on the filter with cold water. After recrystallization from anhydrous alcohol we obtained 2.0 g of the dimethyl ester of 1-cyanomethylpiperidine-2,6-dicarboxylic acid; the m.p. was 110-111°.

Found %: C 55.12; H 6.85.  $C_{11}H_{16}O_4N_2$ . Calculated %: C 54.98; H 6.71.

1-Carboxymethylpiperidine-2,6-dicarboxylic acid (I). 1 g of the diethyl ester of 1-cyanomethylpiperidine-2,6-dicarboxylic acid was boiled with 2.5 ml of 8 N caustic soda for 4 hours. After the solution had cooled, it was acidified with concentrated hydrochloric acid to pH 1.2-1.5, a precipitate being formed. It was recrystallized from water and 0.6 g of 1-carboxymethylpiperidine-2,6-dicarboxylic acid was obtained in the form of a colorless fine-crystalline powder with a blue tint. The m.p. was ~250° (decomp.).

The substance was difficultly soluble in cold water and insoluble in ordinary organic solvents.

Found %: C 46.52; H 5.76; N 5.87.  $C_9H_{13}O_6N$ . Calculated %: C 46.75; H 5.67; N 6.06.

Diethyl ester of N,N'-di(p-toluene sulfonyl) piperazine-2,3-dicarboxylic acid (IV). 23 g of the disodium derivative of N,N'-di(p-toluene sulfonyl) ethylenediamine (m.p. 161-163.5°) and then 23 g of the diethyl ester of mesodibromosuccinic acid were added to a solution of 2.9 g of caustic potash in 130 ml of anhydrous alcohol. The mixture was boiled for 4 hours while stirring and was filtered hot. A precipitate was deposited from the filtrate on cooling and was filtered and washed with cold 10% caustic soda and hot water. After it had been recrystallized from anhydrous alcohol the m.p. of diester (IV) was 133-134.5; the yield was 9.2 g. When the reaction was carried out with the racemic dibromosuccinic acid we obtained a substance with the same melting point. A mixed sample showed no depression of the melting point.

Found %: C 53.22; H 5.38; N 5.02; S 11.21.  $C_{24}H_{30}O_8N_2S_2$ . Calculated %: C 53.50; H 5.61; N 5.20; S 11.91.

Hydrolysis of the diethyl ester of N,N'-di(p-toluene sulfonyl) piperazine-2,3-dicarboxylic acid (IV). 14 g of ester (IV) was boiled with 70 ml of concentrated hydrobromic acid (d 1.48) for 4 hours. During this period the solid ester was converted to an oil, and then a crystalline substance was formed; it was filtered and washed thoroughly with water. We obtained 6.3 g of N,N'-di(p-toluene sulfonyl) piperazine-2,3-dicarboxylic acid; after recrystallization from aqueous methyl alcohol (1: 1), the m.p. was 248-249° (decomp.).

Found %: C 50.15; H 4.71; S 13.20.  $C_{20}H_{22}O_8N_2S_2$ . Calculated %: C 49.80; H 4.60; S 13.29.

14 g of the diethyl ester of N,N'-di(p-toluene sulfonyl) piperazine-2,3-dicarboxylic acid was heated in a sealed tube with 60 ml of hydrochloric acid (d 1.19) and 30 ml of glacial acetic acid at 135-140° for 5 hours. The precipitate which formed when the mixture had cooled was filtered and washed with alcohol and ether. We obtained 5.2 g of the dihydrochloride of piperazine-2,3-dicarboxylic acid (III); after recrystallization from hydrochloric acid (2: 1) the m.p. was 215-217° (decomp.).

Found %: C 29.43; H 4.89; Cl 29.13.  $C_6H_{10}O_4N_2 \cdot 2HCl$ . Calculated %: C 29.16; H 4.90; Cl 28.70.

6 g of N,N'-di(p-toluene sulfonyl) piperazine-2,3-dicarboxylic acid was heated with 30 ml of concentrated hydrochloric acid and 14 ml of glacial acetic acid in a sealed tube for 6 hours at 120-130°. We obtained 2.43 g of the dihydrochloride of acid (III) from the reaction mixture; the m.p. was 215.5-217° (decomp.).

1,4-Di(carboxymethyl) piperazine-2,3-dicarboxylic acid (II). 2 g of the dihydrochloride of acid (III) was added to the solution obtained by neutralizing 3.4 g of monobromoacetic acid with 8 N caustic soda, and more alkali was added with stirring at 40°, the pH of the solution being kept at about 10-11. After the solution had stood overnight it was acidified with concentrated hydrochloric acid to pH 1-2 and the slimy precipitate was filtered and washed with water. We obtained 1.82 g of complexon (II); after this had been recrystallized from water and dried in a vacuum desiccator over  $P_2O_5$  the m.p. was 206-208° (decomp.).

Found %: C 41.69; H 5.08; N 9.45.  $C_{10}H_{14}O_8N_2$ . Calculated %: C 41.34; H 4.86; N 9.64.

Resolution of N,N'-di(p-toluene sulfonyl) piperazine-2,3-dicarboxylic acid (V) into its isomers. A solution of 0.66 g of the cinchonine base in 60 ml of anhydrous methanol was added to a solution of 1.08 g of acid (V) in 30 ml of anhydrous methanol. A precipitate came out on standing, and was filtered and washed with hot methanol. We obtained 0.46 g of the salt; the m.p. was 215-215.5°.

Found %: C 64.97; H 6.22; N 7.99.  $C_{20}H_{22}O_8N_2S_2 \cdot 2C_{19}H_{22}ON_2$ . Calculated %: C 65.03; H 6.21; N 7.85.

The salt obtained was thoroughly triturated with 4 ml of hydrochloric acid (1: 1). The flocculent precipitate was filtered, and then washed with hydrochloric acid and water until a negative reaction was obtained for chlorides. The residue was treated with 10% caustic soda and extracted with a large amount of ether; the aqueous layer was separated and acidified with hydrochloric acid. The precipitate formed was washed with water and was twice reprecipitated by water from alcohol. Acid (V) was obtained; the m.p. was 251-252° (decomp.),  $[\alpha]_D -14.5^\circ \pm 1^\circ$  (in alcohol).

Found %: N 5.73.  $C_{20}H_{22}O_8N_2S_2$ . Calculated %: N 5.81.

#### SUMMARY

1. The cyclic analog of cyanotriacetic acid-1-carboxymethyl-piperidine-2,6-dicarboxylic—was synthesized from the dimethyl ester of piperidine-2,6-dicarboxylic acid; it is assumed that this analog has a trans-configuration.
2. The diethyl ester of trans N,N'-di(p-toluene sulfonyl) piperazine-2,3-dicarboxylic acid was obtained by the reaction of the disodium derivative of N,N'-di(p-toluene sulfonyl) ethylenediamine with the ethyl esters of meso and racemic dibromosuccinic acid; the configuration of this synthesized product was proven by resolution of the corresponding acid into the optical antipodes.
3. The dihydrochloride of trans-piperazine-2,3-dicarboxylic acid was obtained by saponification of trans-N,N'-di(p-toluene sulfonyl) piperazine-2,3-dicarboxylic acid and its diethyl ester; the cyclic analog of ethylenediamine-tetraacetic acid—trans-1,4-di(carboxymethyl)-piperazine-2,3-dicarboxylic acid—was synthesized from this product by condensation with bromoacetic acid in the presence of alkali.

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# REDUCTION OF NAPHTHOL CARBOXYLIC ACIDS

## IV. INDIRECT ELECTROLYTIC REDUCTION OF 2,3-NAPHTHOL CARBOXYLIC ACID IN WATER AND METHANOL

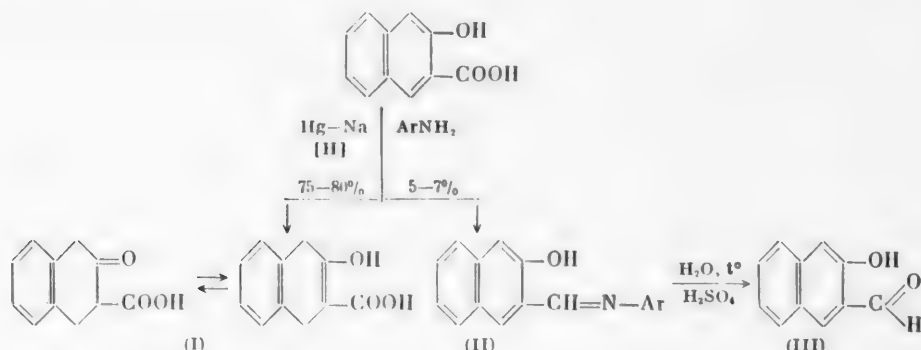
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As previously reported [1], under conditions of indirect electrolytic reduction\* in water in the presence of boric acid, 2,3-naphthol carboxylic acid is hydrogenated in the ring, forming 2,3-tetralone carboxylic acid (I) with a 60% yield.

Continuing the investigation of this reaction we established that simultaneously with hydrogenation of the ring there is also a low degree of reduction of the carboxyl group to an aldehyde group. The yield of 2,3-hydroxynaphthaldehyde (III) precipitated in the form of a Schiff's base (II) is 5-7%.

These additional data make it possible to propose a more complete system of reduction of 2,3-naphthol carboxylic acid under the above-mentioned conditions:



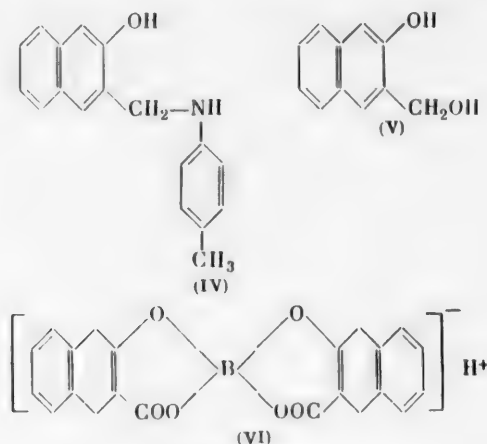
Certain modifications of the reduction process (replacement of 18% hydrochloric acid by carbonic acid) and in the separation of the reaction products made it possible to increase the yield of 2,3-tetralone carboxylic acid to 75-80%. The decomposition temperature of the acid was increased during this process to 135-137° (compared with the previous range of 110-113° [1]). Attempts to increase the yield of 2,3-hydroxy-naphthaldehyde (increase in the amine concentration, replacement of water by methanol) were unsuccessful.

When the reduction is carried out in methanol in the presence of p-toluidine the Schiff's base (II) formed, being present in solution, is further reduced at the double bond  $>\text{C}=\text{N}-$  with formation of 2-hydroxy-3-(N-p-tolylamino-methyl) naphthalene (IV). In the absence of p-toluidine, 2,3-hydroxynaphthaldehyde is reduced to 2-hydroxy-3-hydroxymethylnaphthalene (V).

The structure of compounds (IV) and (V) was confirmed by special experiments on the reduction of 2,3-hydroxynaphthaldehyde (III) and the Schiff's base (II) under these conditions.

\*Reduction by sodium amalgam, formed directly at the mercury cathode during the electrolysis of caustic soda.

When 2,3-naphthol carboxylic acid was reduced in methanol in the presence of p-toluidine, in addition to the above-mentioned compounds (I, IV) we also obtained a complex of 2,3-tetralone carboxylic acid and boric acid, the structure of which, by analogy with the complex obtained in the case of salicylic acid [2], may be represented by structure (VI). When this complex was decomposed,  $\beta$ -tetralone was obtained.



## EXPERIMENTAL

### Reduction in water

The activity of the isoxazole ring in the iodination reaction, as far as we can judge it from the yields of iodides, is in general high and varies somewhat in going from one substituted isoxazole to another. The reactivity of the ring falls in the order 3,5-diphenylisoxazole  $\geq$  3-methyl-5-phenylisoxazole  $>$  3,5-dimethylisoxazole  $\geq$  5-phenylisoxazole  $>$  5-methylisoxazole  $>$  3-phenylisoxazole, which agrees well with the results obtained earlier in our laboratory on chloromethylation [11] and bromination [5].

The reduction was carried out in the same apparatus and with the same procedure as described in [1, 3], the difference being that a further 5 g of aniline (or 5.3 g of p-toluidine) was added to the reaction mixture and the medium was kept slightly acid by passing carbon dioxide through the solution. When reduction had been completed the reaction mass was filtered. The precipitate and the filtrate were treated separately.

**2,3-Tetralone carboxylic acid (I).** The filtrate was acidified with 10% sulfuric acid; the precipitate formed was filtered at the pump, washed with water, dried in air and treated with ether. The ethereal solution was separated from the boric acid and washed with a saturated solution of sodium bicarbonate (5-6 times, 30 ml each). The bicarbonate extracts were acidified with 10% sulfuric acid. The precipitate formed was filtered at the pump and dried; the decomp. temperature was 135-137°. The yield was 7.5-8 g (75-80%).

**Anil of 2,3-hydroxynaphthaldehyde (II).** The precipitate was treated with ether. The ethereal solution was separated from the boric acid and its salts, washed twice with 10% sulfuric acid and then with water, and dried over calcined sodium sulfate. After distillation of the ether, the residue (0.7 g) crystallized into a yellow-green mass. Recrystallization from alcohol gave yellow needles with a m.p. of 157-158°. According to literature data [4], the m.p. is 158-159°. The yield was 5.2%.

Found %: N 5.78, 5.84.  $C_{17}H_{13}ON$ . Calculated %: N 5.66.

**The precipitation of the Schiff's base with p-toluidine** was carried out in a similar way. Plates with a gold luster (from alcohol), m.p. 187-189°. The yield was 1 g (7.5%).

Found %: N 5.29, 5.18.  $C_{18}H_{15}ON$ . Calculated %: N 5.36.

**2,3-Hydroxynaphthaldehyde (III).** 1 g of aniline was steam distilled from solution in 30% sulfuric acid. 0.65 g of a yellow substance was distilled; the m.p. was 97-99°. Recrystallization from glacial acetic acid gave large rhombic crystals with a m.p. of 99-100°. According to literature data [4], the m.p. is 99-100°.

**Oxime.** Crystals with a mother-of-pearl luster, m.p. 208-209° (from alcohol). According to literature data [4], the m.p. is 207°.

**2,4-Dinitrophenyl hydrazone.** Fine, lustrous red needles (from m-xylene), m.p. 300-301°.

Found %: N 16.29, 16.40.  $C_{17}H_{12}O_5N_4$ . Calculated %: N 15.91.

## Reduction in methanol

### a) In the presence of p-toluidine

Reduction was carried out in an electrolyzer, the inner vessel of which had a lid with a hole for stirring and introducing the material. A solution of 15 g of 2,3-naphthol carboxylic acid, 50 g of boric acid and 8.5 g of p-toluidine in 500 ml of methanol was reduced for 3.5 hours at a current strength of 5.5 amp.

Complex of 2,3-tetralone carboxylic acid with boric acid (VI). The reaction mass was extracted from the electrolyzer and filtered from the small colorless precipitate (0.5 g), which did not melt below 300° and gave a positive reaction for boron. The filtrate was mixed with 1 liter of water, acidified with 10% sulfuric acid and treated several times with ether. During this process a colorless fine-crystalline precipitate collected at the ether-water boundary. The ethereal extracts were combined with the precipitate. The precipitate was filtered. The decomp. temperature was 235-237°; it had an odor of  $\beta$ -tetralone. The reaction for borine was positive.

The yield of compound (VI) varied in the individual experiments from 2-4 g (13-26%).

Found %: C 67.80, 68.05; H 5.38, 5.16;  $B_2O_3$  8.75, 8.76.  $C_{22}H_{13}O_6B$ . Calculated %: C 68.00; H 4.37;  $B_2O_3$  9.02.

To decompose complex (VI) to  $\beta$ -tetralone, 3 g of substance (VI) was heated to 230-240° in a test tube with a side-arm. The mass became swollen and dark; the baryta water in which the side-arm was immersed became turbid. When liberation of carbon dioxide had ceased, the viscous mass was transferred to a flask and steam distilled. The distillate (700 ml) was treated with ether. After the ether had been distilled, a light-colored liquid was obtained ( $n_D^{18}$  1.5602).

The m.p. of the 2,4-dinitrophenyl hydrazone was 149-150° (from alcohol).

For  $\beta$ -tetralone  $n_D^{18}$  was 1.5598 [5]; according to literature data [1], the m.p. of the 2,4-dinitrophenyl hydrazone is 147-148°. A mixed melt with the known compound showed no depression of the melting point.

2-Hydroxy-3-(N-p-tolylaminomethyl) naphthalene (IV). The ethereal solution obtained after separation of complex (VI) was treated several times with a saturated bicarbonate solution, washed with water and dried. After the ether had been distilled, 1.0-1.5 g of a dark precipitate was obtained. The precipitate was diluted with a small amount of carbon tetrachloride. The yellow crystals were filtered at the pump and recrystallized from carbon tetrachloride; the m.p. was 178-179°. The substance was readily soluble in alcohol and benzene. An alcoholic solution of the substance gave a greenish-brown color with ferric chloride.

A mixed melt of compound (IV) with the compound obtained by immediate indirect electrolytic reduction of the Schiff's base of 2,3-hydroxy-naphthaldehyde with p-toluidine showed no depression of the melting point. The yield of hydrogenated Schiff's base (IV) is 4.7-7%.

Found %: C 82.18, 82.01; H 6.66, 6.59; N 5.66, 5.78.  $M$  266.0.  $C_{18}H_{17}ON$ . Calculated %: C 82.11; H 6.51; N 5.32.  $M$  263.3.

2,3-Tetralone carboxylic acid (I). The bicarbonate extracts were acidified with 10% sulfuric acid. The yield of acid was 5-7 g (33-47%); the decomp. temperature was 135-137°.

### b) In the absence of amine

Reduction was carried out by the above-described method, but without p-toluidine.

2,3-Tetralone carboxylic acid (I). The reaction mass was treated with 1 liter of water and acidified with 10% sulfuric acid. The flocculent precipitate was extracted with ether. The ethereal solution was treated with a saturated solution of sodium bicarbonate. The bicarbonate extracts were acidified with 10% sulfuric acid. The precipitate of 2,3-tetralone carboxylic acid formed had a decomp. temperature of 135-138°. The yield was 6-8 g (40-53%).

2-Hydroxy-3-hydroxymethylnaphthalene (V). The ethereal solution obtained after treatment with bicarbonate was washed with water and dried. After the ether had been distilled, the residue (2 g) crystallized. After the addition of carbon tetrachloride the yellow crystals were separated and washed on the filter with carbon tetrachloride. We obtained 1 g of substance with a m.p. of 183-185°. Recrystallization from benzene gave fine cream-colored crystals with a m.p. of 188-189°. The yield was 7.3%. According to [6] the m.p. is 189.5-190.5°. An alcoholic solution of the substance gave a green color with a ferric chloride; it gave a red color with concentrated  $H_2SO_4$ . The reaction with 2,4-dinitrophenylhydrazine was negative.

Compound (V) was identical with the compound obtained by indirect electrolytic reduction of 2,3-hydroxynaphthaldehyde immediately.

Found %: C 75.85, 75.68; H 5.76, 5.84.  $C_{11}H_{10}O_2$ . Calculated %: C 75.83; H 5.78.

#### SUMMARY

1. 2,3-Naphthol carboxylic acid was subjected to indirect electrolytic reduction in water in the presence of aromatic amines (aniline and p-toluidine). It was shown that together with 2,3-tetralone carboxylic acid (75-80%), a Schiff's base, 2,3-hydroxynaphthaldehyde (5-7%), is formed in this reduction.
2. It was established that replacement of water by methanol does not have an important effect on the reduction of 2,3-naphthol carboxylic acid.
3. It was shown that 2,3-hydroxynaphthaldehyde in methanol is reduced to 2-hydroxy-3-hydroxymethylnaphthalene; in a similar manner the Schiff's base of this aldehyde is hydrogenated at the C=N double bond.
4. The complex of 2,3-tetralone carboxylic acid with boric acid was isolated and characterized.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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# STUDIES IN THE ISOXAZOLE SERIES

## XII. IODINATION AND BROMINATION OF ISOXAZOLES

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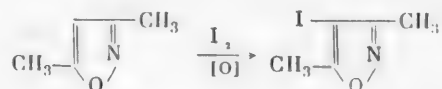
pp. 2326-2333, July, 1961

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We recently succeeded for the first time in obtaining organic magnesium compounds of the isoxazole series [1], which widened very greatly the variety of synthetic possibilities in this field. In this connection it becomes of obvious interest to work out suitable methods for obtaining isoxazole halides, especially iodoisoxazoles, which can serve as starting materials for metalloorganic syntheses, and we have devoted a special investigation to this subject, the results of which are reported in the present paper.

Halogen derivatives of the isoxazoles were obtained [2] by the action of chlorine and bromine on methylisoxazole by illumination or by heating. Recently N. K. Kochetkov and E. D. Khomutova have carried out bromination of isoxazole itself and also of 3- and 5-phenylisoxazoles by bromine in the presence of iron powder, and in all cases they obtained only the 4-bromine substituted isoxazoles [3-5]. Several 4-haloisoxazoles, including the single iodide described in the literature, 3,5-dimethyl-4-iodoisoxazole, were synthesized through the diazo compounds from the corresponding amines [6,7]. However, aside from the length of this three-step process (nitration, reduction and diazotization), this cannot be general, since nitration of phenylisoxazoles usually occurs with substitution of the benzene ring [3,8].

As we reported briefly earlier, we have succeeded in obtaining 3,5-dimethyl-4-iodoisoxazole in high yield by iodination of 3,5-dimethylisoxazole in the presence of nitric acid [1]. This method of halogenation in the presence of an oxidizing agent, new for the isoxazole series, was studied in detail by us, and extended to various substituted isoxazoles, and was also used for obtaining bromoisoxazoles. The optimum reaction conditions were chosen in the case of iodination of 3,5-dimethylisoxazole. As the oxidant we used concentrated nitric acid ( $d_{4} 1.5$ ), a mixture of concentrated sulfuric and nitric acids (nitrating mixture) and 30% hydrogen peroxide. For comparison we also tried to iodinate in the presence of anhydrous ferric chloride. The results of the experiments, carried out under standard conditions, namely, heating the reaction mixture on a boiling water bath, are given in Table 1.



In all the experiments except the iodination in the presence of the nitrating mixture, which was carried out in acetic acid, we did not use solvents.

As the results in Table 1 show, the best results were given by the use of concentrated nitric acid ( $d_{4} 1.5$ ); the use of the nitrating mixture which was previously recommended for the reaction of iodination of aromatic compounds [9] gave a lower yield of iodide. On heating 3,5-dimethylisoxazole with iodine in the presence of ferric chloride we found an intense sublimation of iodine and did not obtain even a trace of iodide, and carrying out this process in an ampule by the method of Meyer [10], because of a too violent course of the reaction, resulted in an explosion. It was established that the best results were obtained at mole ratio isoxazole: iodine: nitric acid = 1:1: 0.5: 1.1.

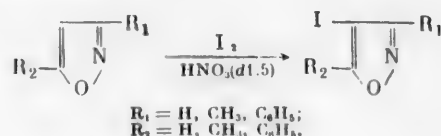
The observed conditions were used further for iodination of other substituted isoxazoles, as a result of which we obtained high yields of the corresponding iodides (Table 3).

TABLE 1

## Iodination of 3,5-Dimethylisoxazole

Oxidant or catalyst	No. of moles added per 1 mole iodine	Reaction time (hours)	Yield, %
30% H <sub>2</sub> O <sub>2</sub>	4,4	10	33
Nitrating mixture	2,2*	1	54-56
HNO <sub>3</sub> (d 1.5)	2,2	1	71-78
Anhydrous FeCl <sub>3</sub>	1	10	—

\*Calculated on the nitric acid.



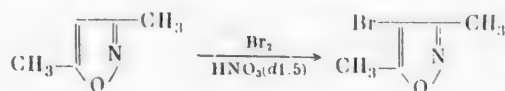
Thus, the reaction of iodination of isoxazole derivatives by iodine in the presence of nitric acid is a sufficiently general and suitable method of obtaining iodoisoxazoles for preparative use. In the case of arylisoxazoles we can consider the possibility of iodination in the phenyl ring. For an explanation of this question the iodoarylisoxazoles which we obtained were oxidized with aqueous solutions of potassium permanganate; in all cases we found only benzoic acid without any admixture of iodobenzoic acid. It follows from this that substitution occurs only in the isoxazole ring; the structure of the iodination product of 3,5-dimethylisoxazole as a 4-substituent was shown earlier by us by converting it to 3,5-dimethylisoxazole-4-carboxylic acid [1]. Since in the isoxazole series all reactions of electrophilic substitution known at the present time always lead to a 4-derivative, we assume for all our iodides the structure of a 4-iodo substituted isoxazole. Direct evidence of this is the production from them of the corresponding acids through the magnesium organic compounds or the preparation of known products of their decomposition, which will be the subject of following communications.

The activity of the isoxazole ring in the iodination reaction, as far as we can judge it from the yields of iodides, is in general high and varies somewhat in going from one substituted isoxazole to another. The reactivity of the ring falls in the order 3,5-diphenylisoxazole  $\geq$  3-methyl-5-phenylisoxazole  $>$  3,5-dimethylisoxazole  $\geq$  5-phenylisoxazole  $>$  5-methylisoxazole  $>$  3-phenylisoxazole, which agrees well with the results obtained earlier in our laboratory on chloromethylation [11] and bromination [5].

The iodoisoxazoles which we obtained are colorless crystalline substances with a specific odor, subliming when heated, easily soluble in most organ solvents, insoluble in water. When kept, only the 3-methyl-4-iodo-5-phenyl- and 3,5-diphenyl-4-iodoisoxazoles are stable; the other iodides slowly turn yellow in the dark, and do so more rapidly in the light.

This method of halogenation of the isoxazole ring in the presence of an oxidant was also used for the synthesis of bromoisoxazoles, which are also needed for detailed study of the magnesium organic synthesis in the isoxazole series.

On repeating the method of the Italian authors [2] by heating 3,5-dimethylisoxazole with bromine at 100° and irradiating with ultraviolet light, we obtained 3,5-dimethyl-4-bromoisoxazole with a total yield of about 27%, and we observed a strong tarring of the reaction mixture. Strong tarring also occurred in bromination in the presence of a catalyst, iron powder [3,5], although in this case the yield was considerably higher. However, the best results were given by brominating 3,5-dimethylisoxazole with bromine in the presence of concentrated nitric acid (cf. [12]). The reaction, as in the case of iodination, took place quickly and smoothly and did not require excess bromine; this method can be recommended as the most suitable with respect to preparation in obtaining the bromoisoxazoles.





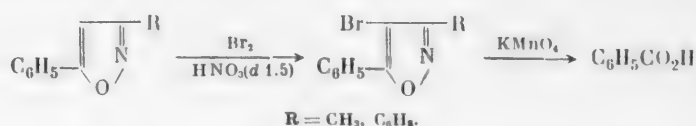
The data on bromination of 3,5-dimethylisoxazole under different conditions is given in Table 2.

TABLE 2

Bromination of 3,5-Dimethylisoxazole

No. of moles isoxazole per 1 mole bromine	Reaction conditions	Yield, %	
		on isoxazole used	on isoxazole reacting
2	Ultraviolet irradiation, 100°, 2 hours	17	27
1.5	50-55°, 2 hours	32	43
1.5	Fe (powder), 50-55°, 2 hours	27	48
1	Fe, 100°, 10 hours	52	52
2.2	HNO <sub>3</sub> (d 1.5), 100°, 0.5 hour	63	63

The possibility of applying this method of bromination to other isoxazoles was shown by us in the case of obtaining the previously undescribed 3-methyl-4-bromo-5-phenyl- and 3,5-diphenyl-4-bromoisoxazole (yield 70%).

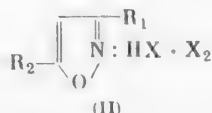
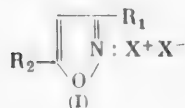


Under these cases substitution also occurs only in the isoxazole ring, as is shown by oxidation of the bromides with permanganate where only benzoic acid is isolated.

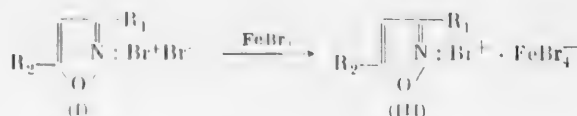
In conclusion we can make some suggestions as to the mechanism of the reaction of isoxazole halogenation on the basis of the facts at our disposal, although we have not specially studied the question of the mechanism.

As is well known, nitrogen-containing heterocycles form with halogens complexes of differing composition. Thus, for pyridine there are descriptions in the literature of complexes of the types  $\text{Py} \cdot \text{Br}_2$  [13],  $\text{Py} \cdot \text{HBr} \cdot \text{Br}_2$ ,  $(\text{Py} \cdot \text{HCl})_2 \cdot \text{I}_2$  [14] and others which are used in organic synthesis for halogenating phenols [15], ketones [16], and in a number of cases are intermediates in halogenation of the heterocyclic systems themselves, as for example in the autohalogenation of pyridine [14]. Analogous complexes are known also for oxazoles [17]. In our experiments on bromination of isoxazoles under different conditions we also found formation of complexes which because of their very great instability could not be studied in detail. Other authors have reported the formation of such substances [2, 18]. Direct evidence of the existence of complexes of isoxazole with iodine would hardly be possible, since iodine-containing complexes are very unstable and could not be isolated even for pyridine [13], though the appearance of the characteristic brown color on mixing isoxazole with iodine in acetic acid showed their formation.

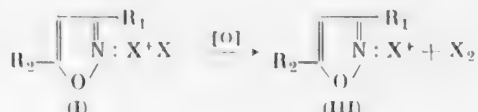
Evidently complexes of isoxazole with halogens (iodine, bromine) of type I are halogenating agents in the reaction under consideration and in the absence of a catalyst carry out intermolecular electrophilic substitution, on which the reaction occurs in this case considerably more easily (2 hours at 50°, see Table 2) than for pyridine, because of the greater activity of the isoxazole ring, which has been observed by us several times in previous communications [3-5, 11]. Also, in distinction from pyridine, because of the lower basicity of the isoxazole ring [19] hydrogen halides are not firmly bound by isoxazoles and therefore, although we can find complexes of type (II) which can also carry out halogenation, yet they are very easily decomposed with evolution of hydrogen halide.



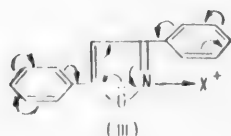
On addition of brominated iron as a catalyst [3,5] a complex is formed whose cation (III) is a brominating agent, and therefore the bromination reaction is facilitated.



The action of the oxidant in the halogenation reaction is evidently analogous and leads to facilitating the occurrence of cation (III) from the complex (I) by oxidizing the halide anion.\*



Thus, evidently, in all cases of halogenation of isoxazoles by true halogenating agents there is a complex cation (III). This suggestion is confirmed by the data which we have obtained. Thus, for example, the identical course of the halogenation reaction for arylisoxazoles and the absence of substitution in the phenyl nucleus finds a natural explanation in the supplementary deactivation of the aromatic ring in the complex cation (III), as is evident in the scheme.



It is evident that the supplementary effect of the positively charged halide connected with the nitrogen is sufficiently great, since our experiments showed that even on halogenation of 3,5-diphenylisoxazole with double the amount of halogen (bromine, iodine) only the 4-haloisoxazole is formed with a yield of 80-90% and does not contain a trace of a product halogenated in the phenyl nucleus. We should mention here that the absence of substitution products in the phenyl nucleus shows the unsuitability in this case of a mechanism suggested for halogenation of aromatic compounds in the presence of nitric acid which goes through a complex aromatic compound with a nitronium cat-

ion [12,20], since nitration of phenylisoxazoles leads to p-nitrophenyl derivatives [2,5], and in our case should also give compounds which contain iodine in the phenyl nucleus.

Our suggested mechanism of isoxazole halogenation also agrees with the fact that bromination occurs with more difficulty than does iodination and especially requires a higher temperature. This fact can be explained, evidently, by the greater oxidizing potential of bromine as compared to the potential of iodine. Finally, the relatively small yield of iodide on iodination in the presence of hydrogen peroxide (see Table 1) is evidently caused by the unsuitable pH of the medium, the value of which, as is known, determines the rate of oxidation by hydrogen peroxide of the iodine anion, especially in complexes of type (I). In this case halogenation occurs by the original complex (I) itself, which is naturally less active as a halogenating agent (cf. [16]).

The ideas developed in this paper on mechanism cannot be considered to be strictly proved, but, as they agree with the experimental facts, they can be considered likely enough.

\* We should keep in mind that because of the excess of isoxazole with respect to halide in our method there can occur in the reaction mixture complexes of type (IV), known in the pyridine series [14]. This, however, does not contradict the point of view expressed here.

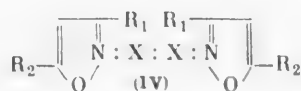
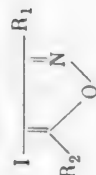


TABLE 3

## 4-Iodoisoxazole



R <sub>1</sub>	R <sub>2</sub>	Empirical formula	Solvent (ml)		Reaction time (hours)	Method of separation	Yield, %	M. p. (solvent for crystallization)	Found %		Calculated %	
			CH <sub>3</sub> CO <sub>2</sub> H	CCl <sub>4</sub>					C	H	C	H
C <sub>6</sub> H <sub>5</sub>	H	C <sub>9</sub> H <sub>6</sub> ONI	10	10	12	I	24	95.5-96.5° (from methanol)	40.00, 40.07	2.63, 2.58	39.87	2.23
H	CH <sub>3</sub>	C <sub>4</sub> H <sub>4</sub> ONI	20	5	14	I	47	28-29 (sublimation)	22.85, 22.88	1.91, 2.01	22.99	1.93
H	C <sub>6</sub> H <sub>5</sub>	C <sub>9</sub> H <sub>5</sub> ONI	—	5	6	I	71	30-32 (from hexane)	40.11, 40.31	2.40, 2.48	39.87	2.23
CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>10</sub> H <sub>8</sub> ONI	10	5	0.5-1	II	80	69.5-71.5 (from hexane)	41.86, 41.97	2.68, 2.76	42.12	2.83
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>15</sub> H <sub>10</sub> ONI	20	5	0.5-1	III	81 (81)••	171-172 (from methanol)	52.21, 51.99	3.10, 3.07	51.90	2.90

• Method of isolation: I, analogous to isolation of 3,5-dimethyl-4-iodo-isoxazole by method C; II, described below for obtaining 3-methyl-4-bromo-5-phenylisoxazole; III, described below for obtaining 3,5-diphenyl-4-bromoisoxazole.

•• At a ratio of reagents 1: 1: 2.2.

## EXPERIMENTAL

**3,5-Dimethyl-4-iodoisoxazole. A.** To a solution of 37.3 g of iodine in 31.3 g of 3,5-dimethylisoxazole with energetic stirring and heating on a boiling water bath was added dropwise 13.6 ml of nitric acid (d 1.5). Then the reaction mixture was heated for 30 minutes more (decoloration then occurred), cooled, the crystals which precipitated were filtered off, washed on the filter with 10% NaOH solution free from slight admixtures of nitroisoxazole, then with water, and dried. Yield 49-55.5 g (71-78%), m.p. 51.5-53°.

**B.** In an analogous way we added to a solution of 4.85 g of 3,5-dimethylisoxazole, 5.7 g of iodine and 3.5 ml of sulfuric acid (d 1.84) in 20 ml of acetic acid, 1.5 ml of nitric acid (d 1.4); we obtained 6-6.2 g (54-56%) of iodide with m.p. 51.5-53°.

**C.** A mixture of 4.85 g of 3,5-dimethylisoxazole, 6.35 g of iodine and 12.5 g of 30% hydrogen peroxide was heated for 10 hours on a boiling water bath with energetic stirring. The lower layer was separated and the water was extracted with chloroform; the combined extracts were washed with a solution of sodium thiosulfate to decoloration, then with water, and were dried over CaCl<sub>2</sub>. After distillation of the solvent and the residue of starting isoxazole we obtained 3.7 g (33%) of iodide with m.p. 51-53°.

3,5-Dimethyl-4-iodoisoxazole after two sublimations in a vacuum had m.p. 51.5-53°; according to the literature [6], m.p. 52.5-54°.

**4-Iodoisoxazoles.** To a solution of 0.015 mole of substituted isoxazole and 0.007 mole of iodine in 10 ml of acetic acid with addition of 5 ml of carbon tetrachloride and energetic stirring and heating on a boiling water bath we added dropwise 0.015 mole concentrated nitric acid. Then the reaction mixture was heated for several hours more, cooled, and after the corresponding treatment the iodide was separated.

**3,5-Dimethyl-4-bromoisoxazole.** In a manner analogous to the iodination by method A we heated for 30 minutes 10.6 g of 3,5-dimethylisoxazole, 2.6 ml of bromine and 4.6 ml of nitric acid (d 1.5), whereupon the reaction mixture was decolorized; then it was diluted with water, extracted with chloroform, the extract washed with 10% NaOH solution and dried over CaCl<sub>2</sub>. After distillation of the sol-

vent, the residue was vacuum distilled and we collected the fraction with b.p. 53-56° (9 mm) and  $n_D^{22}$  1.4870. Yield 12 g (63%). According to the literature [2], b.p. 62° (20-25 mm),  $n_D^{23}$  1.4893.

**3-Methyl-4-bromo-5-phenylisoxazole.** A solution of 2.2 g of 3-methyl-5-phenylisoxazole, 0.32 ml of bromine and 0.6 ml of nitric acid ( $d$  1.5) in 20 ml of acetic acid was heated for 45 minutes, after which the solution became colorless. After distillation of the solvent in a vacuum, the residue was dissolved in chloroform, washed with soda solution and with water and dried over  $CaCl_2$ . The solvent was distilled off and the residue was distilled in a vacuum, with collection of the fraction with b.p. 91-95° (1 mm). After repeated distillations we obtained 2.32 g (71%) of bromide with b.p. 91-92° (1 mm) and with m.p. 24-25° (from *n*-pentane). Fine, colorless needles, easily soluble in benzene, acetone, ether and chloroform, poorly so in methanol and ligroin, insoluble in water. On keeping, it slowly turned yellow.

Found %: C 50.42; H 3.81.  $C_{10}H_8ONBr$ . Calculated %: C 50.43; H 3.39.

**3,5-Diphenyl-4-bromoisoxazole.** A solution of 3 g of 3,5-diphenylisoxazole, 0.32 ml of bromine and 0.6 ml of nitric acid ( $d$  1.5) in 20 ml of acetic acid was heated for 45 minutes, after which the solution became decolorized and a precipitate appeared. The reaction mixture was cooled to 0°, the precipitate was filtered off, washed on the filter with water, and dried. Yield 3.0 g (74%) of bromide with m.p. 129.5-131.5°. After three crystallizations from methanol, m.p. 132.5-133.5°. Colorless platelets, easily soluble in benzene, acetone and chloroform, less so in methanol and ligroin, insoluble in water. Stable when kept.

From 2.9 g of 3,5-diphenylisoxazole, 0.64 ml of bromine and 1.2 ml of nitric acid we obtained 3.45 g (88%) of bromide which gave no depression of melting point in a sample mixed with the previous one.

Found %: C 60.19, 60.37; H 3.45, 3.35.  $C_{15}H_{10}ONBr$ . Calculated %: C 60.03; H 3.36.

**Oxidation of 4-iodo-5-phenylisoxazole.** We boiled 0.85 g of 4-iodo-5-phenylisoxazole for eight hours with a solution of 2 g of potassium permanganate in 100 ml of water, cooled, filtered the manganese dioxide which precipitated. After evaporation of the filtrate, saturating it with sulfur dioxide, acidifying with hydrochloric acid and cooling, we obtained 0.17 g of benzoic acid with m.p. 121-122°. A sample mixed with known material gave no melting point depression, and the Beilstein test was negative. Not even a trace of iodobenzoic acid was isolated from the mother liquor.

After analogous oxidation of 3-phenyl-4-iodoisoxazole, 3-methyl-4-iodo-5-phenylisoxazole, 3,5-diphenyl-4-iodoisoxazole, and also 3-methyl-4-bromo-5-phenylisoxazole and 3,5-diphenyl-4-bromisoxazole, we isolated only benzoic acid without admixture of halobenzoic acid.

#### SUMMARY

1. We have worked out a general method for the synthesis of 4-iodoisoxazoles by action on substituted isoxazoles of iodine in the presence of concentrated nitric acid.
2. We have shown that bromination of isoxazoles in the presence of concentrated nitric acid is also a suitable method for the synthesis of 4-bromisoxazoles, improving the present methods for preparative purposes.
3. We have suggested a mechanism for the halogenation of isoxazoles.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

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# INDOLE DERIVATIVES

## XL SYNTHESIS OF 5-PYRIDAZO-(4,5-b)-INDOLE

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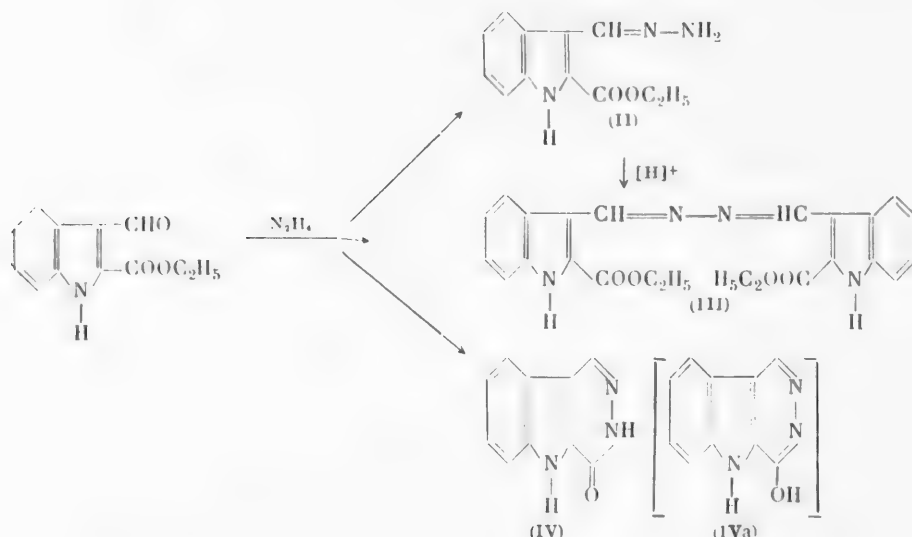
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The condensed systems of indole and pyridazine have hardly been studied. Only some oxygen-containing derivatives of 5-pyridazo-(4,5-b)-indole are known. Thus, King and Stiller [1] by heating 2-carbethoxy-indole-3-aldehyde p-nitrophenylhydrazone in a vacuum at 290-300°, obtained 3-(p-nitrophenyl)-5-pyridazo-(4,5-b)-indol-4-one. Phenyl substituents of this heterocyclic system were described by Staunton and Topham [2]. Among these the system of 5-pyridazo-(4,5-b)-indole is of great interest as the aza analog of carboline, the ring system of which forms the base, as is well known, of many physiologically active compounds including the rauwolfia alkaloids.

In order to study the chemical and pharmacological properties of the pyridazindoles we carried out the synthesis of the first compound of this group, 5-pyridazo-(4,5-b)-indole. The reaction of 2-carbethoxy-indole-3-aldehyde (I) with hydrazine hydrate gave different products, depending on the conditions. When 1 mole of compound (I) was boiled in alcohol with 4.35 moles of hydrazine hydrate it formed the hydrazone of 2-carbethoxyindole-3-aldehyde (II). When the amount of hydrazine hydrate was reduced to 0.725 mole we obtained the corresponding azine (III). It should be noted that the hydrazone easily undergoes symmetrization into the azine by the action of a small amount of acid. Therefore the azine forms, instead of the hydrazone, by the action of aldehyde (I) with hydrazine sulfate. On stepwise addition of a solution of 2-carbethoxy-indole-3-aldehyde (I) to a tenfold excess of hydrazine hydrate in boiling ethyl cellosolve, 5-pyridazo-(4,5-b)-indol-4-one (IV) is formed.



In the infrared spectrum of compound (IV) (Fig. 1), there are bands for the amide carbonyl group (1662 cm<sup>-1</sup>) and the N-H group (3000 cm<sup>-1</sup>) which correspond to the lactam formula (IV) and not the lactim (IVa). These results are confirmed by comparison with the spectrum of 5-methyl-5-pyridazo-(4,5-b)-indolone obtained by a scheme anal-



ogous to that of the synthesis of compound (IV). Its spectrum also contains the bands of the group C=O ( $1662\text{ cm}^{-1}$ ) and N-H ( $3000\text{ cm}^{-1}$ ).

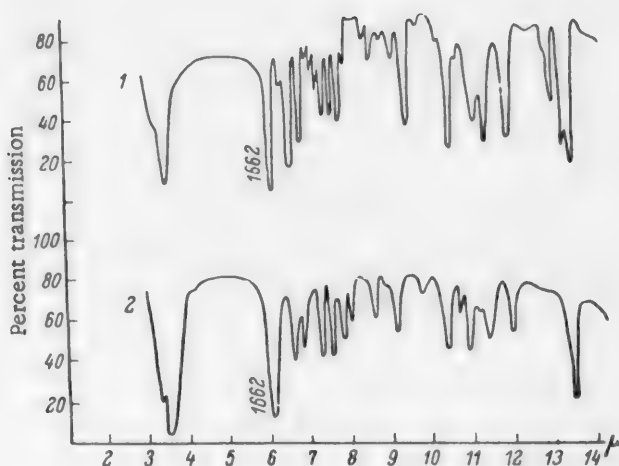
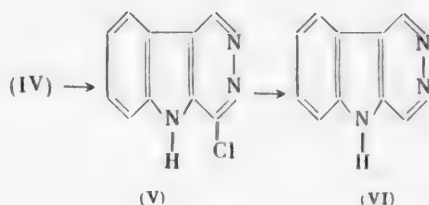


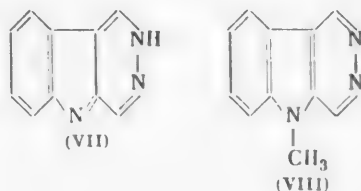
Fig. 1. Infrared absorption spectra. 1) 5-Methyl-5-pyridazo-(4,5-b)-indol-4-one; 2) 5-pyridazo-(4,5-b)-indol-4-one.

Indolone (IV) dissolves with heating in dilute solutions of alkali hydroxides and is reversibly precipitated on acidification. When it is heated with phosphorus oxychloride it forms 4-chloro-5-pyridazo-(4,5-b)-indole (V), the catalytic dechlorination of which over palladium gives 5-pyridazo-(4,5-b)-indole (VI).



The latter is a weak monoacidic base ( $K_a 1.62 \cdot 10^{-6}$ ).• On heating with excess methyl iodide in alcohol, it forms only the monomethiodide.

Since the structure of 5-pyridazo-(4,5-b)-indole, besides formula (VI), could also have the indolenine formula (VII), we compared the spectra of compound (VI) with that of the 5-methyl substituent (VIII). The latter differed from the unsubstituted product by its solubility in water.



• The determination was carried out by L. V. Persianova, to whom we express our thanks.

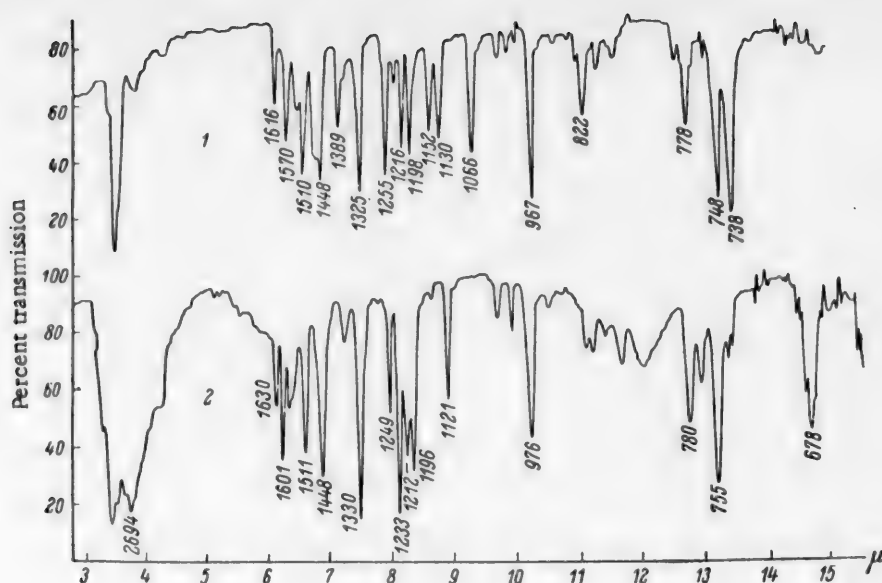


Fig. 2. Infrared absorption spectra. 1) 5-Methyl-5-pyridazo-(4,5-b)-indole; 2) 5-pyridazo-(4,5-b)-indole.

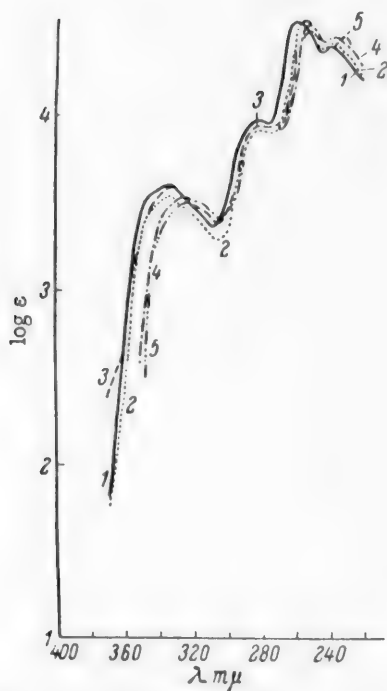


Fig. 3. Ultraviolet absorption spectra. 1) 5-Methyl-4-chloro-5-pyridazo-(4,5-b)-indole; 2) 5-methyl-5-pyridazo-(4,5-b)-indole; 3) 5-methyl-5-pyridazo-(4,5-b)-indole hydrochloride; 4) 5-pyridazo-(4,5-b)-indole; 5) 5-pyridazo-(4,5-b)-indole hydrochloride.

The infrared spectra of 5-pyridazo-(4,5-b)-indole and 5-methyl-5-pyridazo-(4,5-b)-indole (Fig. 2) have in the region of frequencies below  $2000\text{ cm}^{-1}$  a series of common absorption bands analogous in character. A marked difference occurs only in the region from  $2500\text{--}3000\text{ cm}^{-1}$ , where in the spectrum of 5-pyridazo-(4,5-b)-indole there is a wide, intense band from the N-H bond. The ultraviolet spectra of these compounds, like the ultraviolet spectra of the 4-chloro derivative (V), are very similar to each other (Fig. 3). All this shows the indole and not the indolenine structure of the compounds which we have studied.

#### EXPERIMENTAL

**2-Carbethoxyindole-3-aldehyde (I).** *o*-Nitrophenylpyruvic acid was obtained by condensation of *o*-nitrotoluene with diethyl oxalate in the Reissert reaction [3]. Reduction and ring closure to indole-2-carboxylic acid was carried out by the action of ferric sulfate on an ammonia solution of the acid [4]. The ethyl ester of indole-2-carboxylic acid, obtained by the method of Fischer [5] by reaction with dimethylformamide in the presence of phosphorus oxychloride, gave 2-carbethoxyindole-3-aldehyde [6].

**2-Carbethoxyindole-3-aldehyde hydrazone (II).** To a mixture of 0.5 g of 2-carbethoxyindole-3-aldehyde in 13.4 ml of anhydrous alcohol we added 0.5 g (fourfold excess) of hydrazine hydrate. We boiled for three hours. We cooled to room temperature and left the cold mixture to stand for 30 minutes. The precipitate which came down was filtered off and washed with ice cold alcohol. M.p.  $298.5^\circ$  (decomposition, from alcohol and benzene). Yield 0.36 g (67.5%).

Found %: C 62.47; H 5.57; N 18.45.  $\text{C}_{12}\text{H}_{13}\text{O}_2\text{N}_3$ . Calculated %: C 62.34; H 5.64; N 18.20.

**Azine of 2-carbethoxyindole-3-aldehyde (III).** a) To a mixture of 0.3 g of 2-carbethoxyindole-3-aldehyde in 20 ml of alcohol

was added 0,05 g of hydrazine hydrate. The mixture was boiled for three hours; a precipitate came down which was filtered from the hot solution, washed with hot alcohol and with ether. M.p. 315,5° (decomposition, from dimethylformamide). Yield 0,1 g (30,3%).

Found %: C 67,03; H 5,18; N 13,75.  $C_{24}H_{22}O_4N_4$ . Calculated %: C 67,10; H 5,11; N 13,03.

b) We dissolved 0,3 g of 2-carbethoxyindole-3-aldehyde in 20 ml of alcohol with heating and to the hot solution added a hot aqueous solution of 0,72 g (fourfold excess) of hydrazine sulfate in 5 ml of water. At once a yellow crystalline precipitate came down. We boiled for five hours. Then the hot solution was filtered, the precipitate was washed with hot alcohol, water and alcohol. M.p. 316,5-317° (decomposition, from dimethylformamide). Yield 0,3 g (67,4%).

c) A mixture of 0,21 g of 2-carbethoxyindole-3-aldehyde hydrazone, 27 ml of alcohol; and 0,0105 g of p-toluenesulfonic acid was boiled for six hours. It was cooled; the precipitate was filtered and washed with alcohol. M.p. 315° (decomposition, from alcohol). Yield 0,2 g (71,8%).

5-Pyridazo-(4,5-b)-indol-4-one (IV). a) A solution of 2,69 g of 2-carbethoxyindole-3-aldehyde in 243 ml of ethyl cellosolve was gradually added to a boiling solution of 6,15 ml of hydrazine hydrate in 27 ml of ethyl cellosolve during two hours. At the end of the addition the whole solution was heated for one hour. The ethyl cellosolve was distilled off in a vacuum to beginning of crystallization. The resulting precipitate was filtered off and washed with ethyl cellosolve and with ether. M.p. 326,5-327° (from ethyl cellosolve). Yield 2,05 g (89,6%).

Found %: C 64,75; H 3,93; N 22,53.  $C_{10}H_7ON_3$ . Calculated %: C 64,87; H 3,78; N 22,70.

b) We dissolved 0,2 g of 5-pyridazo-(4,5-b)-indol-4-one with heat in 8 ml of 10% sodium hydroxide solution and acidified with a 10% hydrochloric acid solution. M.p. 326,5-327°. Weight 0,2 g. Yield quantitative.

4-Chloro-5-pyridazo-(4,5-b)-indole hydrochloride. To a mixture of 1,35 g of 5-pyridazo-(4,5-b)-indol-4-one in 135 ml of nitrobenzene at 150-155° was added 22,8 ml of phosphorus oxychloride; a precipitate came down at once and after two minutes dissolved. Heating was continued for another 18 minutes (in all, heating lasted 20 minutes from the moment of addition of phosphorus oxychloride). The reaction mass was cooled to room temperature, filtered, washed with nitrobenzene and absolute ether. M.p. 235° (decomposition). Yield quantitative.

Found %: C 49,64; H 2,97; Cl 29,32;  $Cl^-$  15,00.  $C_{10}H_6N_3Cl \cdot HCl$ . Calculated %: C 50,00; H 2,90; Cl 29,62;  $Cl^-$  14,80.

4-Chloro-5-pyridazo-(4,5-b)-indole (V). We dissolved 0,29 g of 4-chloro-5-pyridazo-(4,5-b)-indole hydrochloride with heat in 40 ml of alcohol and added 1,98 g of sodium acetate. The alcohol was distilled off in a vacuum to beginning of crystallization. The resulting precipitate was filtered and washed with water, alcohol and ether. M.p. 272,5-273° (decomposition). Yield 0,16 g (65,3%).

Found %: C 58,82; H 3,22; N 20,49; Cl 17,20.  $C_{10}H_6N_3Cl$ . Calculated %: C 59,01; H 2,97; N 20,61; Cl 17,39.

Picrate, yellow crystals; m.p. 110° (decomposition).

Found %: N 19,05; Cl 8,89.  $C_{10}H_6N_3Cl \cdot C_6H_3O_7N_3$ . Calculated %: N 19,45; Cl 8,24.

5-Pyridazo-(4,5-b)-indole hydrochloride. Five g of 4-chloro-5-pyridazo-(4,5-b)-indole hydrochloride in 1250 ml of alcohol was hydrogenated over 5 g of 10% Pd on carbon at room temperature and 20 atm pressure for 1 hour 35 minutes. The catalyst was filtered off and washed with alcohol. The alcohol was distilled in a vacuum in a stream of nitrogen to beginning of crystallization. M.p. 298-299° (decomposition). Yield 2,63 g (61,5%).

Found %:  $Cl^-$  17,31.  $C_{10}H_7N_3 \cdot HCl$ . Calculate %:  $Cl^-$  17,30.

5-Pyridazo-(4,5-b)-indole (VI). One g of 5-pyridazo-(4,5-b)-indole hydrochloride was dissolved in 25 ml of distilled water and 10 ml of 25% ammonia was added. The precipitate was filtered off and washed with water to a neutral reaction. M.p. 298,5-299° (decomposition, from alcohol). Yield 0,8 g (97,0%).

Found %: C 71,05; H 4,36; N 23,88.  $C_{10}H_7N_3$ . Calculated %: C 71,0; H 4,14; N 24,80.

Picrate, yellow crystals; m.p. 247,5° (decomposition).

Found %: C 49,23; H 3,30; N 19,67.  $C_{10}H_7N_3 \cdot C_6H_3O_7N_3$ . Calculated %: C 49,0; H 2,51; N 21,10.

**5-Pyridazo-(4,5-b)-indole methiodide.** We dissolved 0.4 g of 5-pyridazo-(4,5-b)-indole with heat in 28 ml of anhydrous alcohol, cooled it to room temperature, and added 3 ml of methyl iodide. The reaction mass was boiled for one hour and then cooled. The precipitate was filtered off and washed with anhydrous alcohol and absolute ether. M.p. 243.5-244.5° (decomposition, from alcohol). Yield 0.37 g (50.3%).

Found %: C 41.88; H 3.88; N 13.08; I 40.88.  $C_{11}H_{10}N_3I$ . Calculated %: C 42.50; H 3.30; N 13.50; I 40.81.

**1-Methyl-2-carbethoxyindole-3-aldehyde.** 1-Methyl-2-carbethoxyindole [7] by reaction with dimethylformamide in the presence of phosphorus oxychloride gave 1-methyl-2-carbethoxyindole-3-aldehyde. M.p. 112.5-113°.

**1-Methyl-2-carbethoxyindole-3-aldehyde hydrazone.** A mixture of 0.5 g of 1-methyl-2-carbethoxyindole-3-aldehyde in 13.4 ml of anhydrous alcohol with 0.44 g of hydrazine hydrate was heated to boiling for three hours. It was cooled to room temperature and allowed to stand for 30 minutes in a freezing mixture. The precipitate was filtered off, washed with ice cold alcohol and absolute ether. M.p. 102° (decomposition).

Found %: C 63.66; H 6.03; N 17.50, 16.85.  $C_{13}H_{15}O_2N_3$ . Calculated %: C 63.60; H 5.11; N 17.13.

**Azine of 1-methyl-2-carbethoxyindole-3-aldehyde.** A mixture of 0.5 g of 1-methyl-2-carbethoxyindole-3-aldehyde and 0.07 g of hydrazine hydrate was boiled for three hours in 13.4 ml of anhydrous alcohol. After 40 minutes, precipitation began. The reaction mass was cooled to room temperature and the precipitate was filtered off. M.p. 239-240°.

Found %: C 67.77; H 5.69; N 11.84.  $C_{26}H_{26}O_4N_4$ . Calculated %: C 68.40; H 5.68; N 11.96.

**5-Methyl-5-pyridazo-(4,5-b)-indole-4-one.** A solution of 5 g of 1-methyl-2-carbethoxyindole-3-aldehyde in 450 ml of ethyl cellosolve was gradually added to a boiling solution of 10.85 g of hydrazine hydrate in 50 ml of ethyl cellosolve in the course of two hours. At the end of the addition the whole solution was heated for one hour more. The ethyl cellosolve was distilled in a vacuum to beginning crystallization. The resulting precipitate was filtered off and washed with ethyl cellosolve and ether. M.p. 282.5-283° (from ethyl cellosolve). Yield 4.2 g (97.5%).

Found %: C 66.31; H 4.51; N 21.32, 21.36.  $C_{11}H_9ON_3$ . Calculated %: C 66.40; H 4.52; N 21.10.

**5-Methyl-4-chloro-5-pyridazo-(4,5-b)-indol-4-one hydrochloride.** To 2 g of 5-methyl-5-pyridazo-(4,5-b)-indol-4-one in 100 ml of nitrobenzene at 140-145° was added 35 ml of phosphorus oxychloride. It was heated for 20 minutes beginning from the moment of addition of the phosphorus oxychloride. M.p. 262.5-263° (decomposition). Yield quantitative.

Found %: Cl 27.06, 27.07.  $C_{11}H_8N_3Cl \cdot HCl$ . Calculated %: Cl 27.80.

**5-Methyl-4-chloro-5-pyridazo-(4,5-b)-indole.** To a suspension of 2.86 g of 5-methyl-4-chloro-5-pyridazo-(4,5-b)-indole hydrochloride in 143 ml of distilled water was added 28.6 ml of 25% ammonia. The resulting precipitate was filtered off, and washed with water to a neutral reaction. M.p. 180.5-181° (decomposition). Yield 1.84 g (78.6%).

Found %: C 60.35; H 3.71; N 19.19; Cl 16.44, 16.43.  $C_{11}H_8N_3Cl$ . Calculated %: C 60.68; H 3.79; N 19.30; Cl 16.35.

Picrate, yellow crystals, m.p. 187.5° (decomposition).

Found %: C 46.21, 45.97; H 2.35, 2.57; N 20.06, 20.21.  $C_{11}H_8N_3Cl \cdot C_6H_3O_7N_3$ . Calculated %: C 46.0; H 2.46; N 18.80.

**5-Methyl-5-pyridazo-(4,5-b)-indole hydrochloride.** One g of 5-methyl-4-chloro-5-pyridazo-(4,5-b)-indole in 300 ml of alcohol was hydrogenated over 1 g of 10% Pd on carbon at 46-50° and 10.7 atm pressure. The catalyst was filtered off and washed with alcohol. The alcohol was distilled in a vacuum in a current of nitrogen to beginning of crystallization. M.p. 305-305.5° (decomposition). Yield 0.72 g (71%).

Found %: Cl<sup>-</sup> 16.02.  $C_{11}H_9N_3 \cdot HCl$ . Calculated %: Cl<sup>-</sup> 16.20.

**5-Methyl-5-pyridazo-(4,5-b)-indole (VIII).** We dissolved 0.72 g of 5-methyl-5-pyridazo-(4,5-b)-indole hydrochloride in 30 ml of distilled water, added 2 g of moist, freshly prepared lead hydroxide, and boiled the reaction mass with stirring in a stream of nitrogen for 5 minutes, then cooled, filtered off the precipitate of lead salt and washed it with a small amount of water. The aqueous mother liquor was saturated with hydrogen sulfide. The precipitate of lead

sulfide was filtered off, and washed with a small amount of water. The aqueous mother liquor was evaporated dry in a stream of nitrogen. M.p. 154-154.3° (from methylethyl ketone). Yield 0.53 g (63.3%).

Found %: C 72.03; H 4.99; N 22.57, 22.41.  $C_{11}H_9N_3$ . Calculated %: C 72.11; H 4.95; N 22.94.

Picrate, yellow crystals, m.p. 251.5° (decomposition).

Found %: C 49.73; H 2.89; N 20.58.  $C_{11}H_9N_3 \cdot C_6H_3O_7N_3$ . Calculated %: C 49.60; H 2.91; N 20.39.

The infrared spectra were taken on an IKS-14 spectrophotometer. The substances were studied in the form of a suspension in vaseline oil.

The ultraviolet spectra were taken on an SF-4 spectrophotometer. We used alcohol as the solvent.

#### SUMMARY

1. We have carried out the synthesis of the first member of the heterocyclic system of 5-pyridazo-(4,5-b)-indoles and its 5-methyl-substituent. On the basis of a comparison of their infrared and ultra-violet spectra we have shown that the first has an indole and not an indolenine structure.
2. We have shown spectroscopically that 5-pyridazo-(4,5-b)-indol-4-one exists in the lactam form.
3. We have established that the reaction of 2-carbethoxyindole-3-aldehyde with hydrazine hydrate, depending on reaction conditions, gives a hydrazone, an azine, or a pyridazoindole. The hydrazone of 2-carbethoxyindole-3-aldehyde is easily symmetrized into the azine by the action of acid.

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# THE REACTION OF TRIETHYL ALUMINUM AND TRIPHENYL ALUMINUM WITH BENZOYL PEROXIDE IN BENZENE SOLUTION

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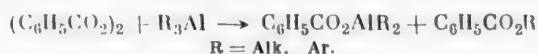
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The reaction of metalloorganic compounds with peroxides has been very little studied. Also this reaction, in our opinion, is of considerable interest, since in the oxidation of metalloorganic compounds there is formed as an intermediate product a compound of a peroxide type [1-3]. The reactions of metalloorganic compounds with acyl peroxides can be divided into the following types.

1. Addition of the benzoyl peroxide to metals with change in their valence [4]. Example  $R_3Bi \rightarrow R_3Bi(OCOC_6H_5)_2$ .
2. Reaction with compounds which contain the bond metal-metal, occurring with rupture of this bond which results in formation of a benzoate derivative of the metal [5]. This holds true for Sn-Sn, Pb-Pb.
3. Reaction of benzoyl peroxide with organomagnesium and organolithium compounds [6,7] accompanied by addition of radicals and metals by oxygen.

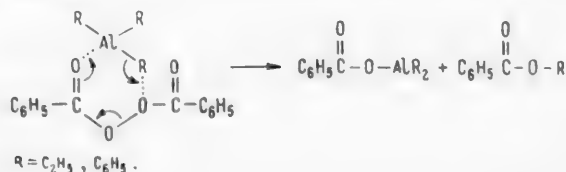
For metalloorganic compounds of aluminum, the properties of which have now been studied by many investigators, there is no information in the literature on their reactions with peroxides. We have studied the reaction of triethyl aluminum and triphenyl aluminum with benzoyl peroxide. In a benzene solution these reactions are strongly exothermic. We used external cooling and the reaction took place at 25-35°. Increasing the reaction temperature results in formation of a complex mixture of reaction products which could not be separated. An interesting characteristic of this reaction is that, after energetic reaction of the components at the beginning of the process, it slows down considerably. About 3% of the total amount of benzoyl peroxide does not react with the aluminum organic compound, even with a great excess of the latter and heating to 60°. The reaction takes place without evolution of gaseous products. Benzoyl peroxide reacts with both triethyl aluminum and triphenyl aluminum according to the equation:



In the reaction products we identified, in the first case, diethyl aluminum benzoate with a yield of 75-100% and ethyl benzoate with a yield of 18-40%; in the second case, diphenyl aluminum benzoate (67%) and phenyl benzoate (51%).

The formation of aluminum dibenzoates occurred only after 90 hours' reaction of benzoyl peroxide with triethyl aluminum at 25-35° and several hours heating at 60°. However, the product was not sufficiently pure. The isolation of pure dibenzoate presented great difficulty.

We suggest that in the reaction of benzoyl peroxide with triethyl aluminum and with triphenyl aluminum there is formation of a six-membered reaction complex of the same type as has been suggested [7] for the reaction of tert-butyl perbenzoate with Grignard reagent.





The diethyl aluminum or diphenyl aluminum monobenzoates which are formed do not tend to form a reaction complex with benzoyl peroxide, and therefore dibenzoate derivatives of aluminum are obtained with difficulty.

#### EXPERIMENTAL

Reaction of triethyl aluminum with benzoyl peroxide. Benzoyl peroxide was twice recrystallized from chloroform. Its activity was 98%. Triethyl aluminum was obtained by symmetrization of the sesquibromide. It contained practically no halogen.\*

The reaction of triethyl aluminum with benzoyl peroxide (BP) was carried out at a ratio  $(C_2H_5)_3Al:BP=1:1$  or  $2:1$ . The conditions of the reaction were the same and the reaction products were isolated in the same way; only in the case of the ratio  $(C_2H_5)_3Al:BP=2:1$  we distilled the excess  $(C_2H_5)_3Al$  from the reaction mixture. The results of the experiments are shown in the table.

Experiment	Used in reaction (mole)		Reaction products (mole)				Benzene (mole)
	triethyl aluminum	benzoyl peroxide (BP)	diethyl aluminum benzoate	ethyl benzoate	unreacted BP	unreacted triethyl aluminum	
1	0.040	0.040	0.031	0.007	0.0012	—	1.0
2	0.060	0.036	0.029	0.007	0.0009	0.012	0.9
3	0.082	0.041	0.030	0.019	0.0014	0.034	1.3
4	0.072	0.031	0.028	0.015	—	0.012	1.0

The reaction was carried out in a three neck flask fitted with a reflux condenser, thermometer, inlet for nitrogen and dropping funnel. The system was blown out with nitrogen, then the sample of triethyl aluminum in benzene solution was placed in the reaction flask. Benzoyl peroxide was dissolved in benzene and this solution was added dropwise to the solution of triethyl aluminum with stirring. The reaction flask was cooled from outside with water and ice. The reaction temperature of the mixture was kept in the limits 25-35°. At the end of the addition of the benzene solution of benzoyl peroxide, the reaction solution was allowed to stand for 24 hours at room temperature under nitrogen. In experiment 4 it stood for 90 hours and then was heated three hours at 60°.

Then from the clear, light yellow reaction solution we distilled the benzene in a vacuum and stream of nitrogen. After the main mass of benzene had been distilled off, unreacted benzoyl peroxide precipitated from the solution. It was filtered from the solution under nitrogen and the solution was again distilled in a vacuum. We collected two fractions with b.p. 85-88° (7 mm) and 99-115° (8-7 mm). (In experiment 1, one fraction with b.p. 87-89° at 7 mm.) These fractions were mixtures of triethyl aluminum with ethyl benzoate. (In experiment 1, pure benzoate.) The amount of triethyl aluminum in a fraction was determined after decomposition of it with 10% sulfuric acid from the ethane evolved and from analysis of the sulfuric acid solution for its aluminum content. Ethyl benzoate after decomposition of the fraction by sulfuric acid was extracted with ether. It boiled at 211-212°; its infrared spectrum was identical with the infrared spectrum of pure ethyl benzoate. The colorless solid residue obtained after distillation of triethyl aluminum and ethyl benzoate decomposed in air. Analysis showed that it was diethyl aluminum benzoate, first obtained by Ziegler [8]. This compound was analyzed for content of aluminum, benzoic acid and the ethyl group.

A sample of the substance was decomposed with 10% sulfuric acid. The ethane which evolved was determined volumetrically. The sulfuric acid solution was repeatedly extracted with ether. The ether extract was dried with sodium sulfate, the ether was distilled off and in the residue we identified benzoic acid by melting point and mixed melting point. Aluminum hydroxide was precipitated from the sulfuric acid solution.

Found %:  $C_6H_5COOH$  59.01, 58.38, 58.30; Al 12.78, 12.92, 12.40; ethane 29.40, 29.27, 27.40.  $C_{11}H_{15}O_2Al$ .  
Calculated %:  $C_6H_5COOH$  58.73; Al 13.10; ethane 28.15.

Reaction of triphenyl aluminum with benzoyl peroxide. Triphenyl aluminum with m.p. 228° was obtained by the method of K. A. Kocheshkov and A. N. Nesmeyanov [9]. The reaction was carried out in the apparatus described above. In the reaction flask under a stream of dry nitrogen we placed 60 ml of benzene and 5.18 g of triphenyl aluminum. A solution of 4.65 g of benzoyl peroxide in 60 ml of benzene was added to the benzene suspension of triphenyl aluminum dropwise. Thereupon the precipitate of triphenyl aluminum gradually dissolved. The reaction was car-

\* We express thanks to A. I. Kirilov for performing the experiments on triethyl aluminum for us.

ried out at 35-40° with external cooling of the system by water and with stirring. At the end of benzoyl peroxide addition the solution stood for 24 hours at room temperature under nitrogen. The clear, yellow reaction solution was heated for two hours at 60° for decomposition of unreacted benzoyl peroxide. The benzene was distilled from the reaction solution in a vacuum. After removal of the main mass of benzene the precipitate (3.9 g) was separated from the reaction solution. It was filtered under nitrogen through a glass filter and washed repeatedly with hexane. The hexane extract was combined with the mother liquor. Then the precipitate was dried in a stream of nitrogen. It consisted of colorless, fine needles with m.p. 159-160°. From the content of benzoic acid and aluminum, the substance was diphenyl aluminum benzoate. A sample of substance was dissolved in 10% NaOH. After solution of the sample, the benzene was distilled from the solution and extracted from the aqueous distillate by carbon tetrachloride and nitrated in it. We obtained dinitrobenzene (nonquantitative determination) with m.p. 89° (from ethanol). The alkaline solution was acidified with 10% sulfuric acid and from the acid solution by repeated extractions with ether we removed benzoic acid (m.p. 121°). After this the aluminum was precipitated from the sulfuric acid solution as the hydroxide.

Found %:  $C_6H_5COOH$  40.8, 42.6; Al 8.8, 9.9.  $C_{19}H_{15}O_2Al$ . Calculated %:  $C_6H_5COOH$  40.4; Al 8.9.

The mixture of hexane and benzene solutions obtained in the filtration and washing of the precipitate contained 0.67 g of diphenyl and 2 g of phenyl benzoate. These products were separated by saponification of the phenyl benzoate with 2 N sodium hydroxide solution. Diphenyl was identified by m.p. 69° (from ethanol).

The formation of phenyl benzoate was shown by isolation of phenol and benzoic acid in the hydrolyzate.

#### SUMMARY

The reaction of triethyl aluminum and triphenyl aluminum with benzoyl peroxide in benzene solution occurs with formation of diethyl- and diphenyl aluminum benzoates, and also ethyl benzoate and phenyl benzoate, respectively.

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# THE OXIDATION OF TRIPHENYL ALUMINUM AND PHENYL LITHIUM

G. A. Razuvaev, E. V. Mitrofanova, and G. G. Petukhov

Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 7,

pp. 2343-2347, July, 1961

Original article submitted July 11, 1960

In our previous work [1] we studied the process of oxidation of triphenyl aluminum in benzene by molecular oxygen. With the aid of labeled  $C^{14}$  benzene and triphenyl aluminum we showed that the oxidation products, phenol and diphenyl, were formed with participation of the solvent. The oxidation process occurs not only with triphenyl aluminum but also with the solvent benzene.

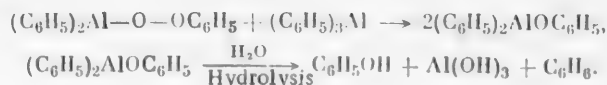
The formation of diphenyl was found also in the oxidation of other metalloorganic compounds, for example, phenyl lithium. It is known that in the oxidation of an ether solution of phenyl lithium there is formed, in addition to phenol, some diphenyl in high yield (65%) [2,3]. The formation of diphenyl in this case undoubtedly occurs because of dimerization of the radicals formed from phenyl lithium. On oxidation of phenyl lithium in benzene we could assume the solvent also shares in the formation of diphenyl. In this case we wish to explain whether oxidation of phenyl lithium in benzene goes with participation of the solvent, as occurs in the oxidation of triphenyl aluminum, and also to study the oxidation of the etherate of triphenyl aluminum in ether.

The oxidation of triphenyl aluminum in ether was carried out at 20° with dry oxygen. We isolated the oxidation products phenol, acetophenone, acetaldehyde, tar and aluminum oxide.

We can assume that the first step in the process is the formation of a metalloorganic peroxide, usual in this type of reaction.



Then the peroxide is reduced by the aluminum organic compound:



On the other hand, similar metalloorganic peroxides are very unstable compounds; they are easily decomposed.

Also, in the process of oxidation the molecules of solvent are affected which were bound to the aluminum organic compound. This explains the occurrence of such products as acetophenone and acetaldehyde.

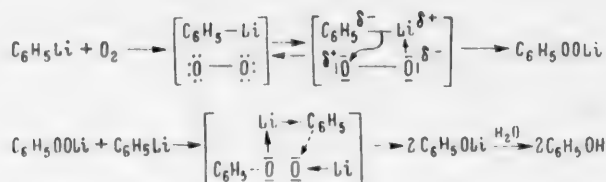
We did not find benzene in the reaction products. Phenylmethyl carbinol, the formation of which might be expected, was also absent.

The oxidation process is very complex as is indicated, for example, by the high yield of products of oxidation (52%).

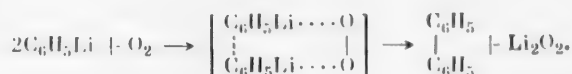
Perhaps there is also further reaction of phenol with oxygen [4].

Oxidation of phenyl lithium in benzene labeled with  $C^{14}$  was carried out in dry oxygen at 20°. The process took place very slowly (about five or nine hours). We isolated two reaction products: phenol (14.4, 19.8%) and diphenyl (14, 20.0%).

The phenol had no labeled atom, but the diphenyl had an activity equal to 12.5% of the starting activity of the benzene. Obtaining inactive phenol and active diphenyl showed that the oxidation of phenyl lithium takes place in two directions. Evidently phenol forms through the hydroperoxide, which reacts further according to the scheme:

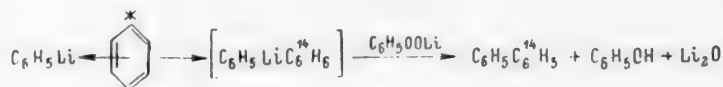


Diphenyl is evidently formed as a result of two processes. The main one can be considered the reaction between two molecules of phenyl lithium and a molecule of oxygen.



In this case we obtain inactive diphenyl.

The second possible process leads to formation of labeled diphenyl by loss of hydrogen and lithium from the intermediate complex of phenyl lithium with lithium benzoyl hydroperoxide.



In this case the diphenyl should bear 50% of the solvent activity. If both processes have the same rate under these conditions, the total diphenyl content would have 25% of the radiocarbon of the benzene. However, we find only 12.5% of the labeled diphenyl. Hence, the first reaction occurs preferentially.

The idea of the possibility of active diphenyl because of reaction of exchange between phenyl lithium and benzene has been rejected because of special experiments described before [5].

#### EXPERIMENTAL

Oxidation of triphenyl aluminum by molecular oxygen in ether solution. Triphenyl aluminum was obtained by the method described earlier [6], m.p. 233°. Ethyl ether was purified according to the method of [7].

Oxidation was carried out in a three neck flask fitted with a reflux condenser, bubbler for admitting dry oxygen [1] and thermometer. The reflux condenser was connected with two traps for removing gaseous reaction products. The traps were cooled with solid carbon dioxide and acetone. Dry nitrogen was blown through the system.

With a counter current of nitrogen we introduced into the flask 170 ml of ethyl ether and (0.0434 mole of) triphenyl aluminum. The triphenyl aluminum, although it could form an etherate, was poorly soluble in ether. Most of it remained undissolved. At 20° in the course of 1.5 hours oxygen was passed into the solution, upon which the temperature rose to 40° and the solid triphenyl aluminum gradually dissolved. The reaction solution became yellow, and then darkened and took on a brownish-black color. After solution of the triphenyl aluminum, a precipitate again came down from the solution; it was aluminum oxide (0.0040 mole). Oxidation stopped after this. The dark ether solution was poured from the precipitate. The precipitate was washed several times with ether which was added to the main ether solution. The  $\text{Al}_2\text{O}_3$  was ignited before weighing. The ether was distilled from the dark ether solution. The residue was a thick, brownish-black liquid (10.2 g). This liquid was treated with a 10% sodium hydroxide solution and steam distilled. Acetophenone distilled off (0.0045 mole) and was separated from the water distillate by ether extraction. The 2,4-dinitrophenylhydrazone had m.p. 220°; a sample mixed with a known acetophenone dinitrophenylhydrazone gave no melting point depression. After removal of the acetophenone, the alkaline solution was acidified with sulfuric acid and phenol was distilled from it with steam. The phenol was identified as tribromophenol, m.p. 93° (from

benzene). Calculated on the phenol we obtained 0,0121 mole. After distillation of the phenol we obtained a tar (1,5 g) from the sulfuric acid solution.

During the process of oxidation of triphenyl aluminum we separated acetaldehyde (0,0005 mole), which condensed in the traps. Acetaldehyde was identified by precipitation of its 2,4-dinitrophenylhydrazone with m.p. 163° and formation of a silver mirror with an ammonia solution of silver oxide.

In the reaction products we found no phenylmethyl carbinol or benzene.

Oxidation of phenyl lithium by molecular oxygen in benzene labeled with  $C^{14}$ . Crystalline phenyl lithium was obtained by the method of [8]. Benzene labeled with  $C^{14}$  (commercial) was purified from unsaturated compounds, dried over sodium, and distilled.

Oxidation was carried out in the apparatus described above. Benzene labeled with  $C^{14}$  was placed in the reaction vessel and the whole system was blown out with dry nitrogen, with passage of the gas through the whole volume of the solution. Then with a counter current of nitrogen a sample of crystalline phenyl lithium was added to the benzene. Oxidation was carried out with dry oxygen which was passed into the system for five or nine hours. The reaction temperature was 20°. Phenyl lithium was practically insoluble in benzene, but as oxygen was passed in, the solid dissolved. The color of the solution changed from light yellow to brown. After oxidation stopped, the dark reaction solution was filtered under nitrogen through a glass filter to remove from it unreacted phenyl lithium and oxides or peroxides of lithium which might possibly have formed. Then the reaction solution was treated with 10% sodium hydroxide solution. Benzene was distilled off on a small column. To the residue we added inactive benzene and again distilled in the column. This operation was twice repeated and was intended to remove traces of labeled solvent from the products which were obtained. After removal of the benzene, diphenyl was separated from the remaining solution. It was dissolved in ether and the solution was steam distilled. Diphenyl was filtered from the aqueous distillate, dried, and recrystallized from ethanol, m.p. 69°. Then we measured its activity on a counter with internal filling. The aqueous alkaline solution was acidified with sulfuric acid and phenol was distilled from it with steam. The phenol was identified as the tribromophenol, which was twice recrystallized from benzene, m.p. 94°. Tribromophenol was analyzed for its activity.

Before oxidation of phenyl lithium in labeled benzene we tested its oxidation in the same apparatus and under the same conditions in inactive benzene. The results are given in Tables 1 and 2.

TABLE 1. Results of Oxidation of Phenyl Lithium in Benzene

Expt. no.	Time of oxidation (hours)	Amount		Reaction products			
		benzene (ml)	phenyl lithium (mole)	phenol (mole)	diphenyl (mole)	yield (%), calculated on phenyl lithium	
						phenol	diphenyl
1	9	50	0,0416	0,007	0,004	20,09	19,8
2	5	70	0,019	0,002	0,0016	15,4	16,2
3	9	50*	0,0416	0,007	0,005	19,8	20,0
4	5	50*	0,0321	0,004	0,0025	14,4	14,1

\* Oxidation of phenyl lithium in benzene labeled with  $C^{14}$ .

TABLE 2. Results of Determination of Activity of Phenol and Diphenyl

Expt. no. (Table 1)	Starting activity $C_6H_6$ (counts/min)	Reaction products			
		Activity of phenol (counts/min)	Activity of diphenyl (counts/min)	percent of starting activity	
				phenol	diphenyl
3	4070	30	500	0,75	12,5
4	3765	31	477	0,8	12,6

\* With participation of E. P. Morozova.

#### SUMMARY

1. Oxidation of the etherate of triphenyl aluminum by molecular oxygen occurs with formation of phenol, acetophene and acetaldehyde. Formation of the last two products shows that the solvent, ether, takes part in the reaction.
2. Oxidation of phenyl lithium by oxygen in benzene labeled with  $C^{14}$  occurs with formation of inactive phenol and partly labeled diphenyl (12.5%), which shows that the solvent, benzene, takes part in the oxidation process.

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# A STUDY OF THE REACTIVITY OF PHENYL LITHIUM USING AN EXCHANGE REACTION

G. A. Razuvaev, G. G. Petukhov, R. F. Galiulina, and  
T. N. Brevnova

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In one of our previously published works [1] we studied the reaction of exchange of phenyl sodium with labeled benzene. It was shown that exchange between phenyl sodium and deuterobenzene occurred very easily at ordinary temperature.

It is known [2] that the C-Li bond in lithium organic compounds has a covalent character, but the reactivity of this class of compounds, especially phenyl lithium, has been little studied. A study of the reactivity of lithium organic compounds is a problem of practical significance; in recent times phenyl lithium has been used as a constituent part of a catalyst in the polymerization of ethylene and formaldehyde [3,4].

In the present work we have set ourselves the problem of studying the exchange reaction of phenyl lithium with radioactive benzene. Along with benzene labeled with  $C^{14}$  we have used  $C_6D_6$  for study of the possibility of exchange of H-D in the system phenyl lithium-benzene in the presence of an alkaline catalyst.

The exchange reaction between crystalline phenyl lithium and labeled benzene was carried out in an ampule sealed in a current of nitrogen with shaking on a shaking machine at room temperature or with heating to 70°. After the exchange the phenyl lithium was converted into benzoic acid by carboxylation.

As the data from the experiments shown in Table 1 indicate, exchange of H-Met in the system phenyl lithium-benzene labeled with radioactive  $C^{14}$  is practically absent (2-4%). Increase in time of running the reaction, and also raised temperature, have no marked effect. The agreement of the results with radioactive and deuterobenzene show that exchange of H-D does not occur in the system.

It is known [5] that phenyl lithium often forms complexes with compounds which contain an atom with a free electron pair. Therefore it seemed interesting to study the effect of such compounds on the exchange. With this in mind, we carried out the reaction in the presence of molar amounts of diethyl ether, dimethylformamide and triethylamine. The results of the study showed that the presence in the system of diethyl ether or dimethylformamide had no marked effect.

However, the results in Table 2 show that in the presence of molar amounts of triethylamine there was a deep exchange.

Under analogous conditions we carried out experiments in the presence of 1, 1/3 and 1/5 mole of triethylamine with respect to 1 mole of phenyl lithium. It was shown that exchange of phenyl lithium with benzene increased with increasing molar amounts of triethylamine. The depth of the exchange depended on time of running the reaction.

In our opinion, the effect of triethylamine on the exchange is explained by the formation of a complex within which exchange occurs by the scheme:

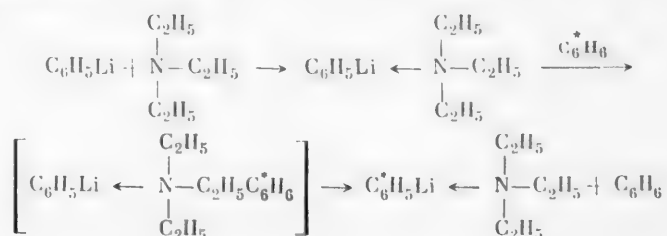


TABLE 1. Study of the Reaction of Exchange between Phenyl Lithium and Labeled Benzene

Reaction components	Temperature	Reaction time, hr	Deuterium content and radioactivity of starting benzene*	Deuterium content and radioactivity of benzoic acid*	Percent exchange
$C_6^{14}H_6 + C_6H_5Li$	14–16°	30	3500	132	3.7
$C_6^{14}H_6 + C_6H_5Li$	70	60	3500	60	1.7
$C_6D_6 + C_6H_5Li$	14–16	47	34000	520	1.5
$C_6D_6 + C_6H_5Li$	70	32	34000	1250	3.6

\*For  $C_6D_6$  the amount of deuterium is given in  $\gamma$ ; for  $C_6^{14}H_6$ , the radioactivity is in counts/min.

TABLE 2. Study of Reaction of Exchange between Phenyl Lithium and Labeled Benzene in the Presence of Triethylamine

Reaction components	Mole ratio of phenyl lithium and triethylamine	Temp.	Time of Expt., hr	Deuterium content and radioactivity of starting benzene*	Deuterium content and radioactivity of benzoic acid*	Percent exchange
$C_6D_6 + C_6H_5Li$	1 : 1	14–16°	37	34000	8220	24
$C_6^{14}H_6 + C_6H_5Li$	1 : 1	70	20	3500	1060	30
	1 : 1/5	70	22	3500	195	5.5
	1 : 1/3	70	22	3970	300	7.5
	1 : 1	70	60	3970	1680	42

\*For  $C_6D_6$  the amount of deuterium is given in  $\gamma$ ; for  $C_6^{14}H_6$ , the radioactivity is in counts/min.

#### EXPERIMENTAL

Crystalline phenyl lithium was obtained by the method of [6] from ethyl lithium and bromobenzene.

The exchange reaction between phenyl lithium and labeled benzene was carried out in ampules sealed in a stream of pure, anhydrous nitrogen. Twenty ml of absolutely anhydrous labeled benzene was placed in an ampule with two outlets, first filled with nitrogen. Then through the open outlet, with a counter current stream of nitrogen, phenyl lithium was added to the ampule in the amount of 1 g. The ampule was sealed and heated at 70° or shaken on a rocker at room temperature (14–16°). In the reaction of phenyl lithium with deuterobenzene we used 1.5 times more phenyl lithium and deuterobenzene.

After the exchange the contents of the ampule were poured out under a stream of nitrogen into a two neck flask with a great excess of solid carbon dioxide. Carboxylation lasted 20–30 minutes, after which the reaction mixture was decomposed with 10% hydrochloric acid. The organic layer was separated from the water; the latter was washed twice with portions of ether, 20 ml. The combined ether extracts were treated with soda solution. The water layer was separated, washed with ether, and evaporated to half volume. Benzoic acid was precipitated with concentrated HCl and extracted from the solution with 20 ml of ether. The benzoic acid after evaporation of the ether was recrystallized from hot water, m.p. 120°. The yield of benzoic acid was not determined; only its isotopic composition was analyzed. The experiments in the presence of the different additives, and also the isolation of benzoic acid after the exchange, were carried out under the same conditions.

Analysis of the compounds studied for content of radiocarbon  $C^{14}$  was carried out by burning the substance to  $C^{14}O_2$ , whose activity was measured on a counter with internal filling. The content of deuterium in the substances studied was determined by the flotation method.

#### SUMMARY

We have shown that exchange between phenyl lithium and  $C_6^{14}H_6$  and  $C_6D_6$  after 60 hours at  $70^\circ$  is practically absent (2-4%).

A study of the effect of diethyl ether, dimethylformamide and triethylamine on exchange between phenyl lithium and labeled benzene was carried out. It was shown that diethyl ether and dimethylformamide had no marked effect on the exchange. In the presence of triethylamine under these conditions there was a deep exchange. The percent of exchange depended on molar amount of triethylamine in the system phenyl lithium-benzene.

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# A STUDY OF THE REACTIONS OF PENTAPHENYL PHOSPHORUS WITH BENZENE USING LABELED ATOMS

G. A. Razuvaev, G. G. Petukhov, and N. A. Osanova

Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 7,

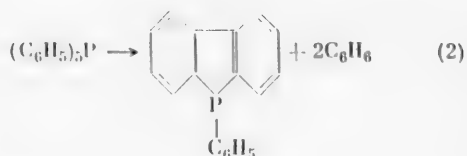
pp. 2350-2353, July, 1961

Original article submitted July 15, 1960

We showed in previous work [1] that pentaphenyl phosphorus can react with solvents in homolytic and heterolytic manner depending on the nature of the solvent. In benzene solution, splitting of the phosphorus compound evidently occurs by a radical mechanism [2]. The main direction of the reaction in this case is the formation of triphenyl phosphine and diphenyl.



Along with this, to a greater or less degree there is a side reaction in which is obtained phenyldiphenylene phosphine and benzene. This reaction in the absence of solvents [3], or in solution in pyridine, is the main one [4].



Evidently, on the basis of equation (1) we cannot definitely say whether the decomposition of  $(\text{C}_6\text{H}_5)_5\text{P}$  takes place with participation of free phenyl radicals or is an intramolecular splitting like reaction (2). This question can be solved with the help of labeled compounds. Such experiments have been carried out in previous work [5]. By experiments with deuterobenzene it was shown that solvents share to a considerable extent in the formation of diphenyl, as is indicated by the presence of deuterium in its composition.

However, it seemed to us that with the use of  $\text{C}_6\text{D}_6$  the appearance of deuterium in the diphenyl could be caused by H-D exchange. Such an effect is excluded if radioactive benzene is used as the solvent. Therefore, in the present work we used  $\text{C}_6^{14}\text{H}_6$  for the study of the reaction of pentaphenyl phosphorus.

On the other hand, in this reaction it is very interesting to explain whether there is an outflow of phenyl radicals of the pentaphenyl phosphorus into the volume of solvent. This could occur because of transfer of identical radicals, as takes place in the decomposition of benzoyl peroxide [6].

Therefore, in a series of experiments we used labeled pentaphenyl phosphorus. Here we considered that formation of a molecule of benzene from a radical of the phosphorus compound also could take place by reaction (2).

In order to explain this question, we carried out experiments on decomposition of labeled pentaphenyl phosphorus in ordinary benzene, and on the other hand, of ordinary phosphorus compound in labeled benzene. The experiments were run in a vacuum system and in the presence of oxygen of the air.

The results of the investigation are given in the table.

As the data of the table (experiments 1-4) show, in the splitting of pentaphenyl phosphorus in radioactive benzene the diphenyl which is formed contains from 5 to 6% phenyl groups of the solvent. The other reaction products, triphenyl phosphine and a tarry substance, do not have active carbon, that is, they are obtained exclusively from the phosphorus compound.

## Results of Isotopic Analysis of Reaction Products of Pentaphenyl Phosphorus with Benzene

Expt. No.	Used in reaction					Experimental conditions	Obtained*										
	pentaphenyl phosphorus			benzene			triphenyl phosphine		diphenyl		benzene		tar				
	structure	amount, g	activity, counts/min	structure	amount, g		activity, counts/min	amount, g	activity, counts/min	activity, %	activity, counts/min	activity, %	amount, g	activity, counts/min			
1	$(C_6H_5)_5P$	{ 2.24 2.5 2.24 2.24	{ — — — —	$C_6^{14}H_6$	{ 4.0 4.6 4.0 4.0	{ 4140 2300 962 962	{ In air  In a vacuum  In a vacuum  In air	0.19	4	0.1	0.15	231	5.6	—	0.8	60	
2								0.17	2	0.1	0.13	103	4.5	—	0.9	15	
3								0.19	2	0.2	0.13	56	5.6	—	0.6	20	
4								0.22	1	0.1	0.15	45	4.7	—	0.7	21	
5	$(C_6H_5)_4PC_6^{14}H_5$	{ 2.5 2.5 3.1	{ 1674 1674 1674	$C_6H_6$	{ 4.6 7.8 4.0	{ — — —	{ In air  In a vacuum  In air	0.39	1630	97.3	0.15	1500	89.6	130	1.1	—	
6								0.21	1630	100.4	0.15	1506	90.0	68	13.4	1.9	1621
7								0.25	1605	95.3	0.23	1570	93.7	160	16.2	1.4	1680
8**								0.85	15580	100.5	0.3	13240	85.5	950	11.6	—	—

\* The percent activity in benzene after reaction was calculated with respect to total content of radiocarbon in the starting compound; the percent activity in the other products was expressed in relative values.

\*\* The deuterium content was given in  $\gamma$ .

These results agree well with those which we obtained in the other series of experiments on decomposition of labeled pentaphenyl phosphorus in simple benzene. Here, besides the reaction products, triphenyl phosphine, diphenyl and tarry substances, we analyzed the benzene isolated after the reaction for content of the carbon isotope. In the case of using deuterium  $(C_6H_5)_4PC_6D_5$  we determined the deuterium content in the reaction products.

As the data in the table show (experiments 5-8), the diphenyl formed consists on the average of only 90% of the phenyl groups of pentaphenyl phosphorus. Ten percent consists of phenyl groups from the solvent. In distinction to the diphenyl, triphenyl phosphine and tar consist entirely of radicals of the phosphorus compound.

In the benzene after the reaction we noted from 12-16% of radioactive molecules formed from phenyl radicals of  $(C_6^M H_5)_5P$ .

The appearance of such a large amount of labeled benzene from fragments of the split substance is explained by occurrence of reaction (2) and the reaction of formation of the tarry substances, which evidently is accompanied by evolution of benzene from the radicals of the phosphorus compound. This is indicated by the fact that in the first experiments with active solvent, as noted above (experiments 1-4), we found in the diphenyl only 5-6% of the phenyl groups of the solvent.

This side direction of splitting of the phosphorus compound in our experiments can be caused by a great concentration of reacting substances.

We should note one more fact, that oxygen of the air has no marked effect on the isotope composition of the products of this reaction (see experiments 4, 7, and 1, 2, 3, 5, 6).

We should also mention that the previously observed equivalence in splitting of all five phenyl groups of pentaphenyl phosphorus [1, 5], as the data of the experiments shows, is well confirmed in the present work.

## EXPERIMENTAL

Pentaphenyl phosphorus  $(C_6H_5)_5PC_6^M H_5$ .  $\frac{1}{2}C_6H_{12}$  with radiocarbon in one phenyl group was obtained from tetraphenyl phosphonium iodide and  $C_6^M H_5Li$  by the method described for the ordinary substance [2, 7]. The m.p. of the substance obtained was 124° (from cyclohexane) with a content of radiocarbon of 1674 counts/min. In the same way, from  $(C_6^9 H_5)_4PI$  and  $C_6^5 D_5Li$  we obtained pentaphenyl

phosphorus  $(C_6H_5)_4PC_6D_5 \cdot \frac{1}{2}C_6H_{12}$  with deuterium in one phenyl group. M.p. 123° (from cyclohexane), containing 15492  $\gamma$  of deuterium.

The compounds  $C_6^{14}H_5Li$  and  $C_6D_5Li$  were synthesized from the corresponding labeled bromobenzene which in turn was obtained from commercial  $C_6^{14}H_6$  and  $C_6D_6$ . The latter were first purified by boiling with  $KMnO_4$  solution and distillation over metallic sodium.

The first part of the experiment on decomposition of pentaphenyl phosphorus in benzene was carried out by heating the reacting components in a flask connected with a reflux condenser.

The other part of the experiment was run in a sealed evacuated ampule in which the reacting mixture was placed.

In both cases heating was carried out on a boiling water bath for 20 hours.

Isolation and purification of the reaction products, triphenyl phosphine, diphenyl and tar, were described in previous work [2].

Analysis for radioactive carbon was carried out by measuring carbon dioxide on a counter with internal filling. The volume of tube was 1.44  $cm^3$   $CO_2$  at normal pressure; working mixture: 40 mm Hg, carbon dioxide and 20 mm Hg n-hexane.

In the table we give the values which show the content of radiocarbon in the  $CO_2$  obtained by burning the substance, which was analyzed.

In the case of pentaphenyl phosphorus  $(C_6H_5)_4PC_6^{14}H_6$  and  $(C_6H_5)_4PC_6D_5$ , it was considered that they crystallized with  $\frac{1}{2}C_6H_{12}$ .

In the carbon dioxide the activity was found directly on the order of 1540 counts/min.

Analysis for deuterium was carried out by the flotation process. The determination was made in the water from burning of the analyzed substance. We found 12910  $\gamma$ .

#### SUMMARY

1. We have studied the splitting of labeled pentaphenyl phosphorus in ordinary benzene and ordinary pentaphenyl phosphorus in radioactive benzene. On heating, the components form diphenyl, triphenyl phosphine and tarry substances. The diphenyl contains 5-6% of the phenyl groups of the solvent. The triphenyl phosphine and tar are obtained exclusively from the phosphorus compound.

2. Splitting of pentaphenyl phosphorus in benzene occurs chiefly by the "cell" reaction. The amount of phenyl radical entering the solvent is 5-6%.

3. Oxygen of the air has no marked effect on the yield and isotope composition of the reaction products.

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# THE INTERACTION OF ETHYLENEIMINOCHLORO BENZOQUINONE-1, 4 WITH ESTERS OF $\alpha$ -ALANINE

A. N. Makarova and A. Ya. Berlin

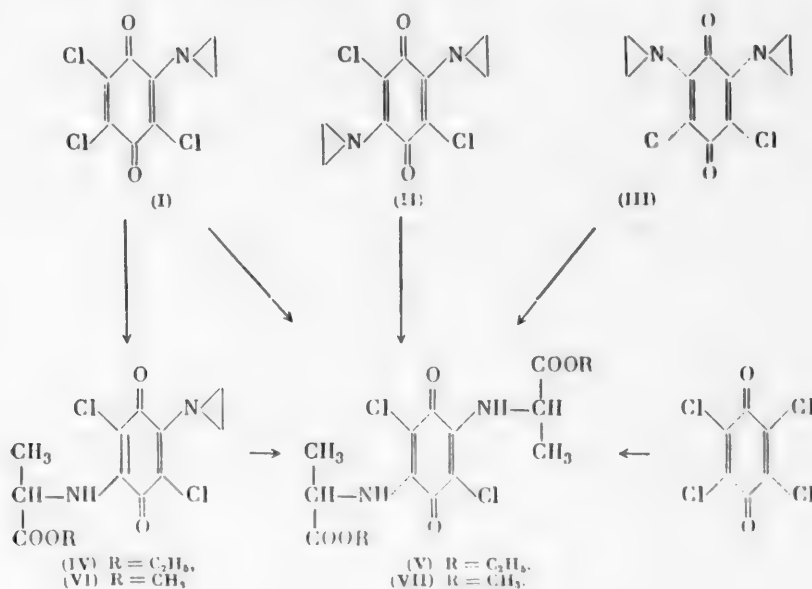
The Institute of Experimental and Clinical Oncology, Academy of Medical Sciences, USSR

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Original article submitted July 4, 1960

In previous papers [1 - 3] we have reported that monoethyleneiminotrichlorobenzoquinone and some substituted 2, 5-diethyleneiminoquinones react with primary amines with the replacement of the ethyleneimino group by the primary amine residues to form the corresponding 2, 5-diaminoquinones. In addition, a rearrangement occurs when 2, 6-diethyleneimino-3,6-dichloroquinone reacts with primary amines; instead of the derivatives of 2,6-diamino-3,5-dichloroquinone, there are formed 2,5-diamino-3,6-dichloroquinones.

We are here reporting a continuation of this work in which we have studied the reaction of monoethyleneiminotrichlorobenzoquinone (I), 2,5-diethyleneimino-3,6-dichlorobenzoquinone (II) and 2,6-diethyleneimino-3,5-dichlorobenzoquinone (III) with the ethyl and methyl esters of  $\alpha$ -alanine.



Monoethyleneiminotrichloroquinone (I) reacts easily with the ethyl esters of  $\alpha$ -alanine to form the diethyl ester of 2,5-di(N-alanino)-3,6-dichloroquinone (V). Apparently the replacement of the chlorine atom which is in the para-position to the ethyleneimino group by the  $\alpha$ -alanine ester residue occurs more easily than the replacement of the ethyleneimino group itself, since by the careful treatment of 1 mole of ethyleneiminotrichloroquinone (I) with 1 mole of the ethyl ester of  $\alpha$ -alanine in alcohol solution there is obtained a 40% yield of the monoethyl ester of 2-(N-alanino)-5-ethylethyleneimino-3,6-dichloroquinone (IV). Under these conditions there is always simultaneously formed the compound with two alanine ester residues (V). Moreover, the monoalanino compound (IV) is easily transformed by reaction with the ethyl ester of  $\alpha$ -alanine into (V).

The picture is approximately the same for the interaction of the monoethyleneiminotrichloroquinone (I) with the methyl ester of  $\alpha$ -alanine. In this case the products are the methyl ester of 2-(N-alanino)-5-ethyleneimino-3,6-dichlorobenzoquinone (VI) and the dimethyl ester of 2,5-di-(N-alanino)-3,6-dichlorobenzoquinone (VII).

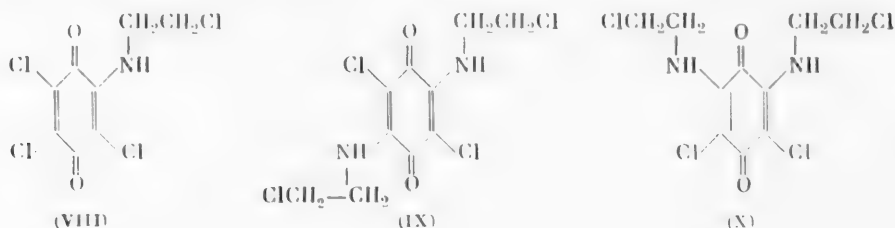
In contrast to monoethyleneiminotrichloroquinone, 2,5-diethyleneimino-3,6-dichlorobenzoquinone (II) and especially 2,6-diethyleneimino-3,5-dichlorobenzoquinone (III) are considerably more inert to reaction with the ethyl and methyl esters of  $\alpha$ -alanine. On long heating both (II) and (III) react with the ethyl ester of  $\alpha$ -alanine to form the same compound – the diethyl ester of 2,5-di-(N-alanino)-3,6-dichloroquinone (V) – in 10–15% yield. All attempts to increase the yield of (V) by changing the conditions of the reaction were unsuccessful.

Thus, the transformation of (III) into (V) is an example illustrating the rearrangement [2] which we observed earlier.

The reactions of (II) and (III) with the methyl ester of  $\alpha$ -alanine occur somewhat more easily and with greater yields of the reaction product – the dimethyl ester of 2,5-di-(N-alanino)-3,6-dichloroquinone (VII). However, the investigation of the compound obtained in this case was made more complex by the fact that it could exist in three crystalline forms: a thermally stable greenish-yellow, a thermally labile greenish-yellow, and a red modification. All three forms, judging from the analytical data, have one and the same composition. The red crystals melt at 178–179°. The thermo-labile greenish-yellow form when heated in a capillary tube gradually changes its external appearance beginning at  $\sim 130^\circ$ , and is transformed into the red form which melts, as indicated above, at 178–179°. The other greenish-yellow form is stable to heat and melts at 142–144°. By recrystallization, all of these forms are convertible into one another with varying ease.

The very same esters of dialaninodichlorobenzoquinone (V) and (VII) are also formed by the interaction of chloranil with the ethyl or methyl esters of alanine.

Thus, the interaction of ethyleneiminochloroquinones with the esters of  $\alpha$ -alanine gives rise to the same regularities of behavior as does the reaction of ethyleneiminoquinones with primary amines [1–3]. By the action of the esters on (I) and (II) the ethyleneimino group is replaced by ester residues. In addition, a rearrangement takes place when (III) is used; an exchange of places between the amino residue and the chlorine atom occurs, followed by the formation of (V) and (VII). When the ethyleneiminoquinones (I), (II), and (III) were treated with hydrochloric acid for the purpose of hydrolyzing the ethyleneimine ring, the behavior of 2,6-diethyleneimino-3,5-dichlorobenzoquinone (III) was especially interesting; we had hoped to obtain without rearrangement 2,6-di-( $\beta$ -chloroethylamino)-3,5-dichlorobenzoquinone. Actually, the action of dilute hydrochloric acid on (I), (II) and (III) easily splits the ethyleneimine ring in all three compounds with the formation of the corresponding  $\beta$ -chloroethylaminotrichlorobenzoquinone (VIII), 2,5-di-( $\beta$ -chloroethylamino)-3,6-dichlorobenzoquinone (IX), and the expected 2,6-di-( $\beta$ -chloroethylamino)-3,5-dichlorobenzoquinone (X) in practically quantitative yield. The formation from (III) of 2,6-di-( $\beta$ -chloroethylamino) compound (X), and not the isomeric (IX), can apparently be explained as due to the introduction of atoms of chlorine into the side chain which leads to a redistribution of the electron density in the quinone molecule. The atoms of chlorine, by drawing the electron to themselves, cause a decrease of the negative charge of the amino group. The carbon atoms in positions 2 and 6 therefore carry a small positive charge [4], and are able to hold onto the  $\beta$ -chloroethylamino residues. The character of the medium in which the reaction occurs also undoubtedly plays a role [5].



#### EXPERIMENTAL

The reaction of ethyleneiminotrichlorobenzoquinone (I) with the ethyl ester of  $\alpha$ -alanine. a) To a suspension of 0.1 g of (I) in methanol was added 0.18 g of the ethyl ester of  $\alpha$ -alanine and the mixture was left at room temper-

ature for 5 hr. A gradual change of color occurred from light red to dark cherry, (I) dissolved, and pink crystals precipitated. After cooling the suspension there was obtained an almost quantitative yield of the diethyl ester of 2,5-dialanino-3,6-dichloroquinone (V): pink needles, m.p. 167-168°.

Found %: C 46.97; H 5.00.  $C_{16}H_{20}O_6N_2Cl_2$ . Calculated %: C 47.19; H 4.95.

b) To a solution of 0.5 g of (I) in 300 ml of methanol was added 0.25 ml of the ethyl ester of  $\alpha$ -alanine and 0.25 ml of triethylamine and the mixture was allowed to stand 2 hr at room temperature. The solution was then evaporated in vacuo while cold to dryness. Fractional crystallization of the residue from ethanol initially yielded 0.1 g (13 %) of the diethyl ester of 2,5-dialanino-3,6-dichloroquinone (V). After removal of (V), the more soluble ethyl ester of 2-alanino-5-ethyleneimino-3,6-dichloroquinone (IV) was obtained from the filtrate. The yield was 0.25 g (40%). Light brown platelets with a mother of pearl luster, m.p. 115 - 116°.

Found %: C 46.68; H 4.33; Cl 21.27.  $C_{13}H_{14}O_4N_2Cl_2$ . Calculated %: C 46.86; H 4.24; Cl 21.28.

To a suspension of 0.1 g of (IV) in methanol was added 0.1 ml of the ethyl ester of  $\alpha$ -alanine. The transformation of the light brown precipitate (IV) into the pink solid (V) began immediately. The yield was almost quantitative.

The reaction of ethyleneiminotrichlorobenzoquinone (I) with the methyl ester of  $\alpha$ -alanine. To a solution of 0.5 g of (I) in 300 ml of methanol was added 0.2 ml of the methyl ester of  $\alpha$ -alanine and 0.2 ml of triethylamine. The solution was left for 0.5 hr at room temperature and then evaporated to dryness in vacuo. Fractional crystallization of the residue from methanol yielded the dimethyl ester of 2,5-dialanino-3,6-dichloroquinone (VII) in three crystalline forms (see below). The yield was 0.15 g (20%). From the filtrate after the separation of (VII) there was obtained the methyl ester of 2-alanino-5-ethyleneimino-2,6-dichloroquinone (VI). The yield was 45%. Brown crystals, m.p. 121 - 122°.

Found %: C 45.35; H 4.05; Cl 21.91.  $C_{12}H_{12}O_4N_2Cl_2$ . Calculated %: C 45.16; H 3.79; Cl 22.22.

The reaction of 2,5-diethyleneimino-3,6-dichlorobenzoquinone (II) with the ethyl ester of  $\alpha$ -alanine. To a suspension at 60-65° of 0.5 g of (II) in 50 ml of ethanol and 0.4 ml of triethylamine was added drop-wise and with energetic stirring a solution of 0.7 ml of the ethyl ester of  $\alpha$ -alanine in 20 ml of ethanol. After 2 hr the mixture was cooled, causing precipitation of 0.42 g of the starting material (II). The diethyl ester of 2,5-dialanino-3,6-dichloroquinone (V) was isolated from the filtrate. The yield was 0.12 g (15%). Extensions of the heating period to 3 and to 6 hr did not lead to an increase of the yield of (V).

The reaction of 2,6-diethyleneimino-3,5-dichlorobenzoquinone (III) with the ethyl ester of  $\alpha$ -alanine. To a suspension at 64 - 65° of 0.7 g of (III) in 70 ml of ethanol and 0.6 ml of triethylamine was added drop-wise a solution of 0.98 ml of the ethyl ester of  $\alpha$ -alanine in 20 ml of ethanol. The mixture was maintained at the indicated temperature with stirring for 9 hr. As in the preceding experiment, 0.15 g of the starting material (III) was recovered and 0.1 g (10 %) of (V).

The reaction of 2,5-diethyleneimino-3,6-dichlorobenzoquinone (II) with the methyl ester of  $\alpha$ -alanine. To a suspension at 48 - 50° of 0.5 g of (II) in 5 ml of methanol was added drop-wise a solution of 4 ml of the methyl ester of  $\alpha$ -alanine in 5 ml of methanol. The mixture was energetically stirred at the stated temperature for 5 hr. After cooling to room temperature, 0.33 g of (II) precipitated. Long cooling of the filtrate yielded a greenish-yellow precipitate. It weighed 0.12 g (16%). The melting point was 132 - 135°. Fractional crystallization of the precipitate from methanol initially yielded tiny red needles with an admixture of the greenish-yellow crystals. Repeated recrystallization of this mixture from methanol yielded tiny greenish-yellow needles (VIIa) which became pink at approximately 130° and melted at 178 - 179°. After removal of the mixture of red and greenish-yellow solids the filtrate yielded a second crop of tiny greenish-yellow needles of a substance which changed on heating in the manner indicated above.

By repeated recrystallization from methanol the greenish-yellow crystals were transformed into the less soluble red needles with m.p. 178 - 179° (VIIb). A test mixture of the red and greenish-yellow crystals did not give a depression of the melting point.

After removal of these two forms the filtrate yielded the greenish-yellow needles of the third stable form, which melted at 142 - 144° (VIIc).

By numerous repetitions of the process — solution of the stable greenish-yellow substance in methanol followed by slow cooling of the solution — it was partially converted into the red substance of m.p. 178 - 179°; this was easily separated because of its lesser solubility.

(VIIa) Found %: C 44.35; H 4.54; N 7.47. (VIIb). Found %: C 44.30; H 4.31; Cl 18.59. (VIIc). Found %: C 44.31; H 4.58; N 7.69; Cl 18.95.  $C_{14}H_{16}O_6N_2Cl_2$ . Calculated %: C 44.33; H 4.25; N 7.39; Cl 18.70.

The reaction of 2,6-diethylenimine-3,5-dichlorobenzoquinone (III) with the methyl ester of  $\alpha$ -alanine. To a suspension at 50° of 0.5 g of (III) in 15 ml of methanol and 0.4 ml of triethylamine was added drop-wise and with good stirring a solution of 0.4 ml of the methyl ester of  $\alpha$ -alanine. The mixture was maintained at 48 - 50° for 5 hr. The recovered (III) weighed 0.4 g; the yield of the three crystalline forms indicated above (VII) was 0.1 g (14%).

The reaction of chloranil with the ethyl ester of  $\alpha$ -alanine. To a solution of 4 g of chloranil in 275 ml of ethyl acetate which was heated on a water bath to 70° was added with stirring 4.5 ml of the ethyl ester of  $\alpha$ -alanine in 15 ml of ethyl acetate. The color of the solution changed from yellow to a dark cherry. The solution was maintained at 70° for 2 hr and then was allowed to stand overnight at room temperature. The precipitate of the hydrochloride of the ethyl ester of  $\alpha$ -alanine was filtered off. The filtrate was evaporated to dryness in vacuo. The crystalline residue was recrystallized from methanol. The product was the diethyl ester of 2,5-dialanino-3,6-dichloroquinone (V). The yield was 3.2 g (50%). The melting point was 167 - 168°.

The reaction of chloranil with the methyl ester of  $\alpha$ -alanine. To a solution of 0.5 g of chloranil in 40 ml of ethyl acetate which was heated on a water bath to a bath temperature of 70° there was gradually added with stirring 0.48 ml of the methyl ester of  $\alpha$ -alanine in 10 ml of ethyl acetate. The light yellow solution became dark cherry. The precipitation of needle shaped crystals soon began. The hydrochloride of the methyl ester of  $\alpha$ -alanine was filtered off after 2 hr, the filtrate was evaporated to dryness in vacuo, and the residue was recrystallized from methanol. The dimethyl ester of 2,5-dialanino-3,6-dichloroquinone (VII) was obtained in three crystalline forms. The yield was 0.35 g (46%). Test mixtures of these forms with the corresponding substances formed from (I), (II) and (III) with the methyl ester of  $\alpha$ -alanine (see above) did not show melting point depressions.

$\beta$ -chloroethylaminotrichlorobenzoquinone (VIII). The substance (I), 0.1 g, was thoroughly triturated with 7 ml of 5% hydrochloric acid; the color of the solid changed from a dark cherry to a reddish-brown. After 2 hr the solid  $\beta$ -chloroethylaminotrichloroquinone (VIII) was filtered off and dried. The yield was quantitative. Dark-brown crystals with m.p. 107 - 108° were obtained after two crystallizations from alcohol.

Found %: C 33.47; H 1.93; N 5.05; Cl 48.78.  $C_8H_5O_2NCl_4$ . Calculated %: C 33.26; H 1.79; N 4.85; Cl 49.08.

2,5-Di-( $\beta$ -chloroethylamino)-3,6-dichlorobenzoquinone (IX). a) The solid (II), 0.1 g, was triturated with 7 ml of 5% hydrochloric acid. After approximately 8 min the entire solid acquired a reddish-lilac color and became voluminous and flaky. After 2 hr at room temperature the solid 2,5-di-( $\beta$ -chloroethylamino)-3,6-dichloroquinone (IX) was filtered off and washed with water, alcohol and ether. The yield was quantitative. After two crystallizations from chloroform the reddish-brown needles had m.p. 209-210° (m.p. 210-210.5° [6]).

b) By titration of 0.1 g of (II) with 7 ml of 18.5% hydrochloric acid a quantitative conversion into (IX) occurred in approximately 4 min.

2,6-Di-( $\beta$ -chloroethylamino)-3,5-dichlorobenzoquinone (X). a) The solid (III), 0.1 g, was triturated with 7 ml of 5% hydrochloric acid. The lilac-color solid was converted in 8 - 10 min to a voluminous and flaky dark green solid. After 2 hr standing the material was filtered off, washed with water, and dried. The yield was quantitative. Two recrystallizations from alcohol yielded dark green crystals, m.p. 129 - 130°.

Found %: C 36.32; H 3.20; N 8.34; Cl 42.52.  $C_{10}H_{10}O_2N_2Cl_4$ . Calculated %: C 36.18; H 3.04; N 8.43; Cl 42.72.

c) Trituration of 0.1 g of (III) with 7 ml of 18.5% hydrochloric acid instantly and quantitatively yielded (X).

#### SUMMARY

1. By the interaction of monoethylenimine-3,5-dichlorobenzoquinone-1,4 with the ethyl and methyl esters of  $\alpha$ -alanine there were obtained the ethyl and methyl esters of 2-(N-alanino)-5-ethylenimine-3,6-dichlorobenzoquinone and also the diethyl and dimethyl esters of 2,5-di(N-alanino)-3,6-dichlorobenzoquinone.

2. The reaction of 2,5-diethyleneimino-3,6-dichlorobenzoquinone-1,4 with the ethyl and methyl esters of  $\alpha$ -alanine yielded the diethyl and dimethyl esters of 2,5-di-(N-alanino)-3,6-dichlorobenzoquinone. The same compounds were also formed from 2,6-diethyleneimino-3,5-dichlorobenzoquinone-1,4 and the ethyl and methyl esters of  $\alpha$ -alanine as the result of a rearrangement.

3. Dilute hydrochloric acid easily splits the ethyleneimine ring of monoethyleneiminotrichlorobenzoquinone, 2,5-diethyleneimino-3,6-dichlorobenzoquinone and 2,6-diethyleneimino-3,5-dichlorobenzoquinone to form, respectively,  $\beta$ -chloroethylaminotrichlorobenzoquinone, 2,5-di-( $\beta$ -chloroethylamino)-3,6-dichlorobenzoquinone and 2,6-di-( $\beta$ -chloroethylamino)-3,5-dichlorobenzoquinone.

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# DERIVATIVES OF PHOSPHOROUS ACID

## II. THE ARBUZOV REARRANGEMENT OF ESTERS OF SALICYLPHOSPHOROUS ACID

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pp. 2358-2362, July, 1961

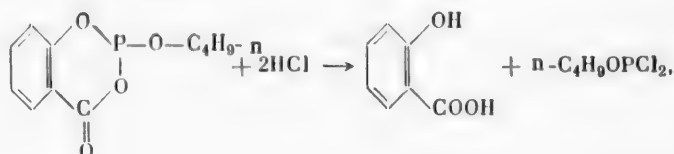
Original article submitted July 22, 1960

The Arbuzov rearrangement of mixed alkyl-aryl phosphites and alkyl-acyl phosphites has been comparatively little studied. In 1940 A. E. Arbuzov and F. G. Valitova [1] isomerized the methyl and ethyl esters of pyrocatechyl phosphorous acid by heating them with the corresponding alkyl iodides. The higher esters (*n*- and isopropyl, *n*- and isobutyl) are not isomerized, but they all enter into the Arbuzov rearrangement with benzyl bromide, splitting off the corresponding alkyl bromide. The ethyl ester of pyrocatechyl phosphorous acid reacts analogously with various triarylmethyl bromides [2]. In 1953 A. E. Arbuzov and L. V. Nesterov [3, 4] studied the interaction of the alkyl esters of diphenyl phosphorous acid with alkyl iodides and found that only the methyl and ethyl esters isomerized; the isomerization does not occur for higher esters.

Very little is known about the rearrangement of the alkyl-acyl phosphites. In 1951 A. E. Arbuzov and P. I. Alimov [5] reported that isovaleryl diethyl phosphite reacted with ethyl iodide to form the isomerization product in small yield (11%). A large yield of a high boiling product of uncertain structure was simultaneously obtained.

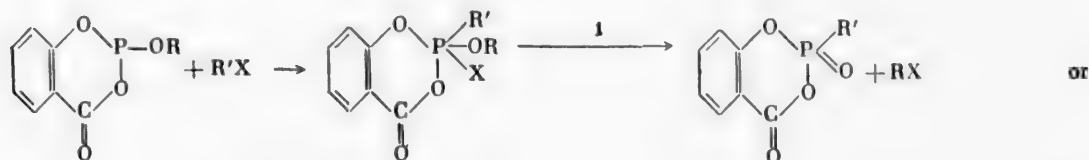
It is the alkyl halide which is split off during the second stage of the rearrangement in all of the cases described, and not aryl halide or acyl halide.

An article by Cade and Gerrard [6] recently appeared in which the reaction of *n*-butyl ester of salicyl phosphorous acid with dry hydrogen chloride was described. The authors isolated the chloroanhydride of *n*-butyl phosphorous acid (26% yield) and salicylic acid (25%) from the products of the reaction. No *n*-butyl chloride was observed. Thus, the reaction went according to the scheme

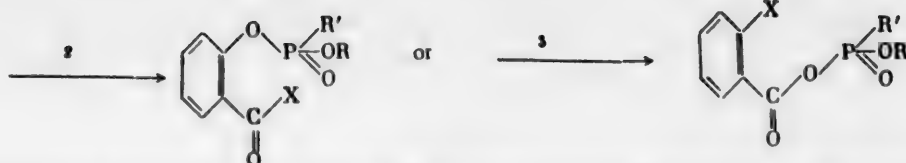


which has nothing in common with the Arbuzov rearrangement.

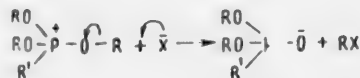
The Arbuzov rearrangement of mixed alkyl-aryl-acyl phosphites has not been studied up to this time. We have carried out the Arbuzov rearrangement with esters of salicyl phosphorous acid [7], which at this time are the only examples of alkyl-aryl-acyl phosphites. One might suggest that the Arbuzov rearrangement of these esters will occur by one of the three possible paths (or by several simultaneously).



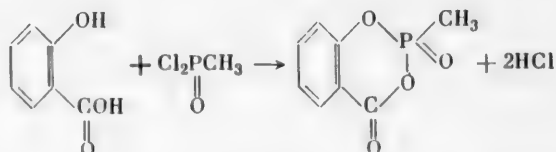




According to the views of Gerrard and Green [8], the second step of the Arbuzov rearrangement has the mechanism:



If the radicals of the intermediate addition product are not equivalent (for example: alkyl, aryl, and acyl), then the alkyl radical must split off most easily with the halogen, since its bond R-O is polarized to a higher degree in the required direction than that of the aryl and acyl. Therefore, path 1 is the most probable for the rearrangement of esters of salicyl phosphorous acid, and this has been confirmed by our experiments. Only the methyl and ethyl esters of salicyl phosphorous acid are isomerized with good yield under these conditions; the higher esters do not react with the corresponding alkyl iodide — after lengthy heating (about 70 hr) at 130° the starting material is recovered unchanged. The salicyl derivatives of methylphosphinic and ethylphosphinic acids were hydrolyzed to give salicylic acid and the free alkyl phosphinic acids. The structure of the salicyl derivative of methylphosphinic acid was confirmed also by a second synthesis from salicylic acid and the chloroanhydride of methylphosphinic acid.



The molecular refraction of the liquid derivative of ethylphosphinic acid was determined ( $\overline{MR}_D$ ) 48.80; calc. 48.32). Although the experimental value exceeds the calculated ( $\Delta \overline{MR}_D$  0.48), the excess is not as large as the exaltation of the salicyl derivative of phosphorous acid, which was determined by us and was equal to 1.12[7]. However, it is impossible to draw any conclusions on the basis of a single example.

That the higher esters of salicyl phosphorous acid are capable of undergoing the Arbuzov rearrangement was shown by reaction of the isobutyl ester of this acid with methyl iodide: the salicyl derivative of methylphosphinic acid and isobutyl iodide were isolated in excellent yield, respectively 83% and 90%. This same ester reacted with benzyl iodide to give an 83% yield of isobutyl iodide. The phosphorous-containing products were partially decomposed by the heat during the distillation of the alkyl iodide and could not be purified.

#### EXPERIMENTAL

The isomerization of the methyl ester of salicyl phosphorous acid. A mixture of 16.4 g of the methyl ester of salicyl phosphorous acid and 11.8 g of freshly distilled methyl iodide was sealed into a glass tube. The tube was heated in boiling water for 20 hr. During the last 5 hr the reaction mixture did not decrease in volume and the reaction was considered finished. When the tube was opened, its contents suddenly crystallized and part of the methyl iodide evaporated at this point. The residual methyl iodide was removed in vacuo (12 mm at room temperature). The crystals (16.4 g, 100%) were washed with ether and dried, m.p. 99–100°; they melted at exactly the same temperature after recrystallization from hot carbon tetrachloride. The substance was quite soluble in hot halogen derivatives (alkyl halides, chloroform, carbon tetrachloride) and in dioxane, but poorly soluble in hydrocarbons (hexane, benzene) and in ether. Its dissolution in water and in alcohol was accompanied by the evolution of heat and chemical change.

Found %: P 15.30.  $C_8H_7O_4P$ . Calculated %: P 15.66.

According to the analytical data, the substance is the salicyl derivative of methylphosphinic acid (2-methyl-5,6-benzo-1,3,2-dioxaphosphorinone-4-oxide-2).

The substance was hydrolyzed by boiling with water for 1 hr. Crystals of salicylic acid (m.p. 155°) were filtered off from the cooled solution. The filtrate was evaporated and was heated in a sealed tube with a large quantity of water to 170° for 5 hr in order to decompose the residual salicylic acid. Methylphosphinic acid (m.p. 101°) was isolated following a second evaporation and several recrystallizations.

The isomerization of the ethyl ester of salicyl phosphorous acid. A mixture of 20.1 g of the ethyl ester of salicyl phosphorous acid and 14.7 g of ethyl iodide was heated in a sealed tube for 40 hr in the vapor of boiling isoamyl alcohol (132°). The contents of the tube were distilled. Ethyl iodide distilled first, followed by 2-ethyl-5,6-benzo-1,3,2-dioxaphosphorinone-4-oxide-2.

B. p. 153° (0.3 mm),  $n_D^{20}$  1.5437,  $d_4^{20}$  1.3397,  $MR_D$  48.80; calculated 48.32.

Found %: P 14.30, C<sub>9</sub>H<sub>9</sub>O<sub>4</sub>P. Calculated %: P 14.62.

The yield was 15.2 g (75.7%) of a colorless, viscous liquid with a weak, but characteristic, odor.

The reaction product was hydrolyzed as in the preceding experiment. Ethylphosphinic acid, m.p. 55°, was isolated.

The reaction of the isobutyl ester of salicyl phosphorous acid with methyl iodide. A mixture of 4.98 g of the isobutyl ester of salicyl phosphorous acid and 4.67 g of methyl iodide (molar ratio 1:1.6) was heated in a sealed tube on a boiling water bath for 25 hr. The reaction was considered finished when the volume ceased to decrease. The tube was placed in a cooling mixture (-15°) and its contents partially crystallized. The cold tube was opened; no pressure was apparent. The liquid phase was distilled and the following fractions were obtained: up to 60°, 0.84 g (impure methyl iodide); 110-126°, 3.43 g,  $n_D^{20}$  1.4975 (isobutyl iodide, 90%); residue, 1.3 g. The crystals in the tube were washed with a small quantity of absolute ether and were dried in vacuo; m.p. 98-99° before recrystallization, m.p. 99-100° after recrystallization from hot carbon tetrachloride. A mixture with the salicyl derivative of methylphosphinic acid melted at 99-100°. The yield was 3.41 g (83%) before recrystallization.

The reaction of the chloroanhydride of methylphosphinic acid with salicylic acid (a second synthesis of 2-methyl-5,6-benzo-1,3,2-dioxaphosphorinone-4-oxide-2). In a round bottomed flask equipped with a reflux condenser were placed 1.92 g of the chloroanhydride of methylphosphinic acid, 1.99 g of salicylic acid (molar ratio 1:1) and 10 ml of dry benzene. The mixture was boiled for 4 hr, at which time the evolution of hydrogen chloride ceased. The benzene was distilled away at 12 mm and 100°. The residue (2.85 g, 100%) crystallized. The substance melted at 99-100° after recrystallization from hot carbon tetrachloride. A mixture with the salicyl derivative of methylphosphinic acid did not give a depression of the melting point.

#### SUMMARY

1. The esters of salicyl phosphorous acid undergo the Arbuzov rearrangement only with the most active alkyl halides.
2. The Arbuzov rearrangement of these esters does not disturb the 6-membered heterocyclic ring which contains 1 atom of phosphorus and 2 atoms of oxygen.
3. The salicyl derivatives of methylphosphinic and ethylphosphinic acids have been obtained for the first time.

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# THE SYNTHESIS OF $\beta$ -(9-ACRIDYL)-ALANINE AND ITS N-OXIDE

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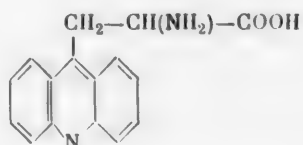
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The important role of  $\beta$ -phenylalanine and certain other natural  $\alpha$ -amino acids in the metabolism of viruses [1-3] has recently become apparent. On this account numerous derivatives of phenylalanine have been synthesized and tested as potential antiviral agents [2, 3]; among these are its heterocyclic analogs [4, 5]. Some of these, for example, the 2- and 3-thienylalanines, have hindered the development of viruses [5].

In connection with this biological testing program we undertook the synthesis of a new heterocyclic analog of  $\beta$ -phenylalanine— $\beta$ -(9-acridyl)-alanine.



Two paths ordinarily used for the synthesis of derivatives of alanine were tested: 1) from the appropriate aldehyde to the azlactone with hippuric acid, followed by hydrolysis of the azlactone and reduction of the unsaturated acid so formed; 2) from the appropriate methyl halide derivative by condensation of the latter with N-acetylamino-malonate (see the scheme).

In both cases the starting material for the synthesis of  $\beta$ -acridylalanine was 9-methylacridine (I), which was obtained either from diphenylamine and acetic anhydride [6] or from 9-chloroacridine and malonic ester [7]. In the first case, 9-methylacridine was converted into acridaldehyde (II) by reaction with p-nitrosodimethylaniline followed by hydrolysis of the azomethine [8]; the latter was then condensed with hippuric acid to form the azlactone (III). Hydrolysis of (III) in aqueous alkali gave N- $\alpha$ -benzoylamino- $\beta$ -(9-acridyl)-acrylic acid (IV). The latter was reduced with hydriodic acid in the presence of red phosphorous. This produced a brown precipitate which investigation showed to be a compound of acridylalanine with red phosphorous. Treatment of this compound with a 10 % ammonia solution precipitated the phosphorous, and from the colorless, alkaline filtrate acridylalanine (VI) was obtained by evaporation to dryness.

The substance gives the characteristic color reaction for amino acids with ninhydrin; however, because of the small stability (instantly becomes pink in air) and the very poor solubility in the majority of organic solvents, the compound could not be purified and identified in the form of the free base. Recrystallization of (VI) from a mixture of alcohol and hydrochloric acid yielded a yellow crystalline substance which was easily soluble in water and decomposed at 220°. The elementary analysis of the latter corresponded with the dihydrochloride of acridylalanine with 1 molecule of water (VII).

Acridylalanine was also obtained by the other method: the bromination of 9-methylacridine with N-bromosuccinimide [7] and condensation of the 9-bromomethylacridine (VIII) with acetylamino-malonic ester. Hydrolysis of the condensation product (IX) with hydrochloric acid yielded a yellow precipitate which after recrystallization from hydrochloric acid appeared to be identical with the dihydrochloride of acridylalanine (VII) already obtained. Neutralization of an aqueous solution of the hydrochloride (VII) with saturated soda solution gave a base of melting point 187-189° with the same composition and properties as the compound (VI).



## EXPERIMENTAL

The azlactone of acridalhippuric acid (III). A mixture of 6.2 g of acridaldehyde, 6.2 g of hippuric acid, 3.1 g of anhydrous sodium acetate and 45.0 ml of acetic anhydride was heated on a water bath for 1 hr. The solid which precipitated on cooling was filtered off and washed with ether; it was then recrystallized with benzene. The azlactone of acridalhippuric acid was obtained in the form of soft lemon yellow needles with m.p. 253 - 255°, 7.45 g (71.2%).

Found %: C 78.61, 78.49; H 4.07, 4.10; N 8.30, 8.19.  $C_{23}H_{14}N_2O_3$ . Calculated %: C 78.86; H 4.00; N 8.00.

N- $\alpha$ -Benzoylamino- $\beta$ -(9-acridyl)-acrylic Acid (IV). The azlactone (III), 3 g, was heated on a water bath for 4.5 hr with 200 ml of a 0.2 % solution of NaOH. The hot solution was filtered, cooled, and acidified with 10% hydrochloric acid until an acid reaction was obtained with Congo Red. The precipitated acid was filtered off, washed with water, and dried.

N- $\alpha$ -Benzoylamino- $\beta$ -(9-acridyl)-acrylic acid was obtained in the form of a finely-crystalline yellow powder with m.p. 257°. The yield was 3.0 g (95.5 %).

The reduction of N- $\alpha$ -benzoylamino- $\beta$ -(9-acridyl)-acrylic acid (IV). To 3.5 g of N- $\alpha$ -benzoylamino- $\beta$ -(9-acridyl)-acrylic acid, 1.81 g of red phosphorous and 11.3 ml of acetic anhydride, 11.3 ml of 50% hydriodic acid was slowly added with stirring, and the mixture was boiled for 3.5 hr. The brick-colored solid which precipitated abundantly when the reaction mixture was cooled was filtered off and washed with a small quantity of cold water; the latter was thoroughly removed on the filter; 20 ml of a 10% solution of ammonium hydroxide was added to the filter cake. After 30 min the residue of red phosphorous was filtered off and the colorless filtrate was evaporated to dryness on a water bath. The residue was carefully washed free of mineral salts with water and was dried to constant weight in a vacuum desiccator at 40°. The yield was 1.23 g (45.8%), m.p. 187-189° (with decomposition). The substance immediately became pink in air and on long standing attained a raspberry color; it gave an intense violet color with ninhydrin, was easily soluble in acids and bases and was practically insoluble in water and organic solvents.

The dihydrochloride of acridylalanine (VII). The solid acridylalanine, 1.5 g, was twice recrystallized from a mixture consisting of various quantities of hydrochloric acid (1:1) and alcohol. The purified material melted at 220° (dec.). The melting point was not raised by further purification. The compound was easily soluble in water, difficultly soluble in alcohol, and did not dissolve in benzene and ether. The base itself, acridylalanine with m.p. 187 - 189°, was obtained by neutralization of the aqueous solution of the dihydrochloride with saturated soda solution.

Found %: C 54.18, 54.00, 53.92; H 5.03, 5.04, 5.11; N 7.83, 8.03, 7.81; Cl 19.65, 19.52.  $C_{16}H_{16}O_2N_2Cl_2 \cdot H_2O$ . Calculated %: C 53.78; H 5.04; N 7.84; Cl 19.61.

The condensation of 9-bromomethylacridine with acetylaminomalonic ester. To an alcohol solution of sodium alcoholate obtained from 20 ml of anhydrous alcohol and 0.25 g of metallic sodium was added with stirring 2.0 g of acetylaminomalonic ester; to the solution thus obtained was rapidly added with heating on a water bath a solution of 2.7 g of 9-bromomethylacridine [7] in 30 ml of dry benzene. The mixture was boiled for 2 hr, filtered from the precipitate of sodium bromide, and the filtrate was evaporated in vacuo. The glassy residue was triturated with 20 ml of absolute ether. A white, finely-divided solid was obtained by this; it was filtered off and washed with ether. The melting point was 132 - 137°. After two recrystallizations from carbon tetrachloride, the substance had a constant melting point of 144.5 - 146.0°. The yield was 2.15 g (53%).

Found %: C 67.22, 67.45; H 5.66, 5.78; N 6.74.  $C_{23}H_{24}O_5N_2$  (IX). Calculated %: C 67.65; H 5.88; N 6.86.

The hydrolysis of the condensation product (IX). A mixture of 2.15 g of the condensation product (IX) just obtained and 5.0 ml of hydrochloric acid (1:1) was boiled for 4 hr. The yellow precipitate which formed on cooling was filtered off and twice recrystallized from a mixture of alcohol and 17.5% hydrochloric acid. The lemon yellow crystalline substance, m.p. 220° (with decomposition), weighed 1.8 g.

Found %: C 54.16, 53.93; H 5.11, 5.08; N 7.91.  $C_{16}H_{16}O_2N_2Cl_2 \cdot H_2O$ . Calculated %: C 53.78; H 5.04; N 7.83.

A test mixture of this substance and the dihydrochloride of acridylalanine (VII) melted at the same temperature. A white substance which rapidly became pink in air was isolated by treatment of the compound with soda solution; the product was identical with the base earlier obtained, acridylalanine (VI.).



The N-oxide of the condensation product of 9-bromomethylacridine with acetylaminomalonate (X). A mixture of 2 g of the condensation product (IX) and 60 ml of a chloroform solution of perbenzoic acid ( $T = 0.017$  g/ml, 1.5 mole excess) was let stand overnight in a refrigerator. On the following day the orange-red solution (with a greenish fluorescence) was filtered from a small precipitate, and the chloroform was evaporated. The dark reddish-brown oil which remained was triturated with a small quantity of ether and the yellow solid which formed was filtered off. The latter was washed with a large quantity of ether in order to remove benzoic acid. The yield was 1.7g (83%). The melting point was 194-196°. The tiny yellow needles melted at 209-210° after two recrystallizations from alcohol.

Found %: C 65.10, 65.24; H 5.76, 5.71; N 6.65, 6.78.  $C_{23}H_{24}O_6N_2$ . Calculated %: C 65.09; H 5.66; N 6.60.

The hydrochloride of the N-oxide of acridylalanine (XI). A mixture of 2 g of the N-oxide (X) and 5 ml of hydrochloric acid (1:1) was boiled for 2 hr. The yellow hydrochloride of the N-oxide of acridylalanine (XI) which precipitated on cooling was twice recrystallized from a small quantity of hydrochloric acid (1:1). The yield of the hydrochloride (XI) was 1.1 g (69%), decomposing at 186 - 190°.

Found %: C 56.78, 56.62; H 4.99, 5.12; N 7.79, 7.82.  $C_{16}H_{15}O_3N_2Cl \cdot H_2O$ . Calculated %: C 57.06; H 5.05; N 8.32.

The substance was quite soluble in water, forming an orange solution which on standing and heating rapidly hydrolyzed, precipitating the yellow N-oxide of acridylalanine.

The N-oxide of acridylalanine (XII). To a solution of 1.1 g of the hydrochloride of acridylalanine in 50 ml of water, diethylamine was added drop-wise to a pH of 7. The yellow N-oxide of acridylalanine precipitated. The substance was stable in air in the absence of unoxidized acridylalanine. The yield of the base was 1.0 g, m.p. 186 - 190° (with decomposition). The substance is poorly soluble in the majority of organic solvents. It was recrystallized from a large quantity of water. The fine yellow needles melted at 203 - 205° (with decomposition) after two recrystallizations.

Found %: C 64.19, 64.21; H 5.46, 5.46; N 9.00.  $C_{16}H_{14}O_3N_2 \cdot H_2O$ . Calculated %: C 64.00; H 5.33; N 9.33.

The catalytic reduction of the N-oxide of acridylalanine. To a suspension of 1.0 g of the N-oxide of acridylalanine (XII) in 50 ml of water was added 2.0 g of freshly prepared Raney nickel, and the mixture was hydrogenated with energetic shaking at room temperature and atmospheric pressure for 4 hr. The catalyst was filtered off, the light pink filtrate was slightly concentrated, 2 ml of concentrated hydrochloric acid was added and the solution was evaporated to dryness. The yellow residue was twice recrystallized from a mixture of alcohol and hydrochloric acid. The hydrochloride of acridylalanine was obtained in the form of lemon yellow crystals with m.p. 219 - 220° (with decomposition), 0.61 g; it was identical with the product of the previous preparation.

#### SUMMARY

1. The synthesis of new heterocyclic analogs of  $\beta$ -phenylalanine was realized:  $\beta$ -(9-acridyl)-alanine and its N-oxide.
2. Seven previously undescribed compounds were isolated and characterized in the course of the synthesis.

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# TRANSESTERIFICATION OF METHYLPHOSPHONITES

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The reaction of transesterification as a method of synthesizing esters occupies an important place in organic chemistry. The aspects of its application to the carboxylate ester series are particularly diverse, and it has been studied in detail in connection with such synthesis. This reaction has not been investigated nearly as well for esters of heteroorganic acids, including esters of the acids of phosphorus. Thus, it is known that phosphates and phosphonates are poorly drawn into the reaction of transesterification, in consequence of which it is used hardly at all for the synthesis of these substances [1, 2]. In contrast to the acids of pentavalent phosphorus, the esters of acids of trivalent phosphorus readily enter into the transesterification reaction. In recent years this method has been applied to the simplest trialkyl phosphites [3], dialkyl phosphites [4] and dialkyl phosphonites [5] to obtain certain esters that are inaccessible or difficultly accessible by other methods. However, this reaction has remained unstudied with respect to clarifying the effect on reaction course of such factors as structure of the ester being transesterified, the hydroxyl component, temperature conditions, etc., and its mechanism has not been elucidated. The absence of such data is explained partially by the fact that earlier investigations of the reaction were concerned with esters containing two or three alkoxy groups.

TABLE 1

Reaction between Monoethyl Ester of Methylphosphonous Acid (5.4 g, 0.05 mole) and Hexanol-1 (5.1 g, 0.05 mole)

Catalyst	Bath temp.	Time, hr	Yield, %
Effect of catalyst			
—	150—180°	15	61
Zn-borate		14	65.3
Na		5	71.5*
ZnCl <sub>2</sub>		5	47
H <sub>3</sub> PO <sub>4</sub> (80%)		5	49.5
AlCl <sub>3</sub>		5	59.5
Effect of temperature			
Na	150—180	5	71.9
Na	130—135	15	47
Na	100	15	39.5
Na	120—125**	5	51.5

\* With molar ratio 0.05: 0.075, yield 60.5%; with ratio 0.05: 0.1, yield 64.8%.

\*\* Pressure 160 mm.

In the present work, transesterification is studied in the instance of acid esters of alkylphosphonous acids and various alcohols; here also there is a clarification of the question as to the influence on yield of various reaction conditions, structure of the alcohol entering into the transesterification, and catalyst. In the transesterification of acid phosphonites only one ester can be obtained, which makes it possible to eliminate the difficulties encountered by previous investigators who used trialkyl and dialkyl esters of acids of trivalent phosphorus.

The phosphonites used in this work were the monomethyl, monoethyl and monoisopropyl esters of methylphosphonous acid. The optimum conditions of synthesis were selected by a detailed study of the reaction of the monoethyl ester of methylphosphonous acid with hexanol-1 (see Table 1).



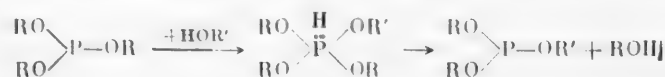
The best results are obtained by conducting the transesterification at 150–160° with 1:1 reactant ratio in the presence of metallic sodium catalyst. The reaction temperature can be reduced somewhat if the process is carried out under slight vacuum. Under optimum conditions (for 5 hours) the transesterification product yields with hexanol-1 constituted 71.5, 64.3 and 44.4%, respectively, for the methyl, ethyl and isopropyl esters of methylphosphonous acid.

Using the optimum synthesis conditions, various esters of methylphosphonous acid were obtained with good yields (see Table 2). Thereby it was demonstrated that the reaction is general for primary and secondary alcohols; it should be noted that the secondary alcohols react considerably more poorly. Attempts to accomplish the transesterification reaction with tertiary alcohols (in the instances of trimethyl carbinol and dimethyl butyl carbinol) were not successful.

TABLE 2  
Acid Esters of Methylphosphonous Acid  $\text{CH}_3-\text{P} \begin{array}{l} \text{OH} \\ \text{OR} \end{array}$  Obtained by Transesterification Method  
(0.05 mole phosphonite per 0.05 mole alcohol; catalyst – sodium; reaction time 5 hours)

Significance of R	Temp. of expt.	Yield, %	Boiling point (pressure in mm)	$n_D^{20}$	$d_4^{20}$	MR <sub>D</sub>		% P	
						found	calc.	found	calc.
n-C <sub>4</sub> H <sub>9</sub>	150–160°	72.0	101–103° (18)	1.4263	0.9978	34.97	35.26	22.91, 23.00	22.80
n-C <sub>6</sub> H <sub>13</sub>	150–180	71.5	117–119 (12)	1.4320	0.9700	43.91	44.50	18.94, 19.05	18.87
n-C <sub>8</sub> H <sub>17</sub>	150–180	65.0	108–111 (2)	1.4378	0.9359	53.79	53.74	15.71, 15.66	16.11
n-C <sub>10</sub> H <sub>19</sub>	150–180	69.0	123–127 (1)	1.4391	0.9305	58.67	58.36	15.084, 15.035	15.01
n-C <sub>10</sub> H <sub>21</sub>	150–180	68.3	132–135 (2)	1.4421	0.9208	63.32	62.98	13.63, 13.70	14.06
Cyclohexyl-	150–180	24.7	117–118 (10)	1.4645	1.6422	42.01	42.30	18.96, 18.82	19.10
(CH <sub>3</sub> ) <sub>3</sub> CCH(CH <sub>3</sub> )	125–130	22.0	92–94 (10)	1.4320	0.9728	43.78	44.50	18.32, 18.22	18.87
sec-Octyl-	160–180	43.5	90–92 (0.5)	1.4334	0.9359	53.41	53.74	15.60, 15.68	16.11

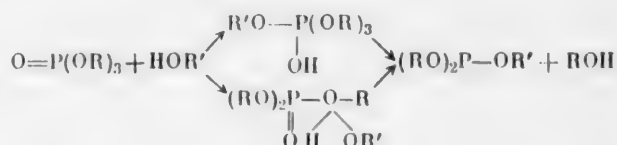
The transesterification reaction of esters of acids of trivalent phosphorus differs in mechanism from the transesterification reaction of carboxylic acids. The decisive factor is the presence of a free pair of electrons on the phosphorus atom. The initial act will be the addition of a proton to the phosphorus and the formation of a phosphonium cation, which with the alcohol moiety gives an unstable product with a 10-electron envelope on the phosphorus.



The addition of the alcohols should proceed with great ease for those esters in which the substituents possess lower electrophilicity. Consequently, with otherwise equal conditions, phosphonites should be transesterified more readily than phosphites. The second act of the reaction will be the splitting of the addition product, which takes

place, not by an Arbuzov-type reaction, but differently, with the formation of a phosphite or phosphonite and an alcohol. The question of which alcohol molecule will be split from the intermediate complex is determined by the same factors applying in the case of transesterification of carboxylate esters.

The transesterification reaction of phosphates and phosphonates, in contrast to the above, are similar in mechanism to the analogous reaction of carboxylate esters. The addition of the alcohol and the formation of an unstable intermediate product in this case will occur at the site of the phosphoryl group ( $P=O$ ) or, less probably, at the free pair of electrons of an ester oxygen atom.



Trialkyl phosphates and dialkyl phosphonates do not enter well into the transesterification reaction, mainly because of difficulty in surmounting the energy barrier in the process of adding the alcohol to the phosphoryl group caused by the slight positive charge on the phosphorus, and because of steric hindrance connected with the large screening effect of the phosphorus atom.

#### EXPERIMENTAL

All experiments on transesterification were conducted under similar conditions. A Claisen flask was charged with a mixture of monoethyl ester of methylphosphonous acid [6] and the appropriate alcohol, and also a small piece of sodium (or other catalyst). The reaction mixture was heated gradually in an oil bath, taking care that the temperature of the material being distilled off in the vapors was not more than  $75-77^\circ$ . The reaction was concluded after close to the calculated quantity of alcohol had been distilled off. (After redistillation, b.p.  $78-78.5^\circ$ ,  $n_D^{20}$  1.3615.) The resulting mixture was vacuum distilled. All operations should be carried out in an atmosphere of pure nitrogen.

#### SUMMARY

The monoesters of methylphosphonous acid enter into the reaction of transesterification with primary and secondary alcohols. A study has been made of the various factors influencing the course of the reaction in the transesterification of monoesters of methylphosphonous acid. A mechanism is proposed for the transesterification reaction of phosphites and phosphonites.

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# TRANSESTERIFICATION OF THE MONOETHYL ESTER OF METHYLPHOSPHONOUS ACID BY GLYCOLS

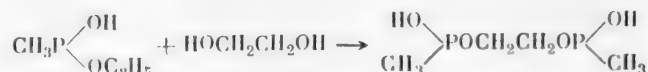
K. A. Petrov, É. E. Nifant'ev, and R. G. Gol'tsova

Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 7,

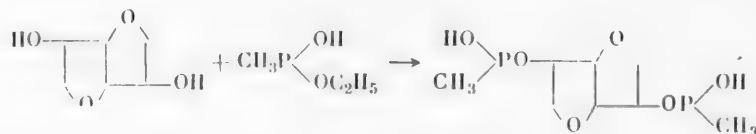
pp. 2370-2373, July, 1961

Original article submitted July 22, 1960

As we have shown previously, the methyl and ethyl esters of methylphosphonous acid are transesterified well by monobasic alcohols; this is a convenient method of synthesis of various acid methylphosphonites [1]. In the present work we have studied the analogous reaction with glycols and have established that the transesterification also proceeds readily and bis-esters of methylphosphonous acid are obtained with good yields, for example:



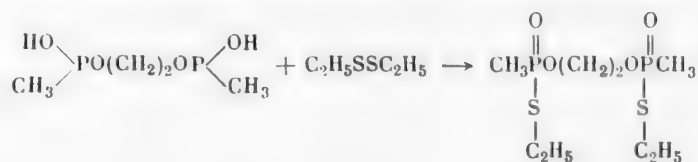
In addition to ethylene glycol, this reaction proceeds with 1,3-propanediol, 1,3-butanediol, diethylene glycol and p-dihydroxymethylbenzene. The transesterification reaction proved to be suitable for the synthesis of complex esters of methylphosphonous acid. Thus, we were successful in obtaining the bis-phosphonite of 1,4,3,6-dianhydromannitol





The latter conversion is interesting in that it leads to a phosphonite containing the mannitol moiety, while no esters of phosphonous acids derived from sugars or related substances had been known previously.

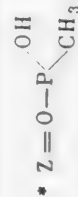
It must be noted that the transesterification of the acid ester of methylphosphonous acid by ethylene with the participation of only one hydroxyl was not carried out successfully; in all cases, even with a large excess of ethylene glycol, only the bis-phosphonite is formed. Evidently this result is related to the fact that on introducing the phosphonous acid radical in place of the hydrogen atom in one of the hydroxyl groups of the ethylene glycol, an additional polarization of the H-O bond in the second alcohol group occurs. Consequently, the free hydroxyl group in the intermediate product of transesterification will display a greater tendency toward interaction with another molecule of the ester of trivalent phosphorus than that of the hydroxyl of ethylene glycol itself. Therefore, the intermediate product enters into reaction with the ethyl ester of methylphosphonous acid more rapidly than does the ethylene glycol itself.

The resulting bis-phosphonites are thick liquids or solid substances, distilling without decomposition only under high vacuum. These compounds are poorly soluble in the majority of the common solvents; the simplest of the compounds are soluble in water and alcohol. The esters of phosphonous acid and glycols in their properties are reminiscent of similar esters formed by monobasic alcohols and acids of trivalent phosphorus. Thus, with one of the esters which we prepared we were successful in carrying out the Jacobson reaction [2], it being found that the diphosphonite reacts with a disulfide at both of its phosphonite groups, forming a dithioldiphosphonate.



# Synthesis of bis-Methylphosphonites of Glycols

Formula *	Yield, %	B. p. (pressure 10 <sup>-4</sup> mm)	n <sub>D</sub> <sup>20</sup>	d <sub>4</sub> <sup>20</sup>	M <sub>R</sub> <sub>D</sub>		% P		% C		% H	
					found	calc.	found	calc.	found	calc.	found	calc.
Z-CH <sub>2</sub> -CH <sub>2</sub> -Z	62.1	85-88°	1.4705	1.2902	40.28	40.52	33.14 33.20	33.29	25.54 25.49	25.76	6.52 6.59	6.46
Z-(CH <sub>2</sub> ) <sub>2</sub> -Z	38.8	95-97	1.4608	1.2147	45.19	45.24	30.58 30.51	30.96	30.05 30.69	30.01	7.23 7.18	7.51
$\begin{array}{c} \text{H} \\   \\ \text{Z}-(\text{CH}_2)_2-\text{C}-\text{Z} \\   \\ \text{CH}_3 \end{array}$	48.2	98-101	1.4627	1.1940	49.38	49.86	—	—	33.36 33.19	33.65	7.79 7.77	7.53
Z-(CH <sub>2</sub> ) <sub>2</sub> O(CH <sub>2</sub> ) <sub>2</sub> -Z	53.0	113-115	1.4694	1.2437	51.57	51.50	—	—	31.53 31.79	31.31	7.30 7.44	7.01
Z-CH <sub>2</sub> -  -CH <sub>2</sub> -Z	20.8	118-123	1.4840	1.1892	63.09	64.53	—	—	45.92 46.20	45.81	5.87 5.70	6.15
	34.0	124-127	1.5087	—**	—	—	22.57 22.75	22.97	35.42 35.31	35.58	5.74 5.82	5.93



\*\*Density could not be determined successfully because of high viscosity.

## EXPERIMENTAL

**Method of Transesterification.** A mixture of the glycol and the monoethyl ester of methylphosphonous acid in a 1:3 molar ratio was placed in a Claisen flask, a small piece of sodium was added, and the mixture was heated in a stream of nitrogen at 160 - 180° for 5 hours; during this time almost all of the theoretically calculated quantity of alcohol distilled off (b.p. 73 - 76°). Then an aspirator pump was connected, and the excess monoethyl ester of methylphosphonous acid was distilled off (b.p. 70 - 71° at 13 mm); the residue was distilled under high vacuum. Yields and constants of the resulting compounds are summarized in the table.

**Synthesis of Dithioldiphosphonate.** A mixture of 9.3 g of the acid ester of ethylene glycol and methylphosphonous acid and 24.4 g of diethyl disulfide was placed in a Claisen flask. The mixture was heated to 110° in a stream of nitrogen, a small piece of sodium was added, and the mixture was heated 5 hours at 140 - 150°; during this time ethyl mercaptan distilled off. Then the excess diethyl disulfide was distilled off (b.p. 71 - 73° at 110 mm). The residue (12 g) was distilled under high vacuum, collecting the 90 - 93° fraction (10<sup>-4</sup> mm). Obtained 4.2 g (35%),  $n_D^{20}$  1.5120,  $d_4^{20}$  1.2720,  $MR_D$  72.38.

Found %: P 20.17, 20.14; S 20.68, 20.57.  $C_8H_{20}O_4P_2S_2$ . Calculated %: P 20.20; S 20.90.  $MR_D$  73.73.

Thick oil, poorly soluble in the majority of organic solvents; under refrigeration it is preserved for a long time.

## SUMMARY

1. Various glycols are readily transesterified by the monoethyl ester of methylphosphonous acid, there being obtained previously unknown acid bis-phosphonites.
2. The interaction of the acid ester of ethylene glycol and methylphosphonous acid with diethyl disulfide leads to the corresponding dithioldiphosphonate.

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# SYNTHESIS OF DIALKYL ACYL PHOSPHITES AND ALKYL ACYL PHOSPHONITES

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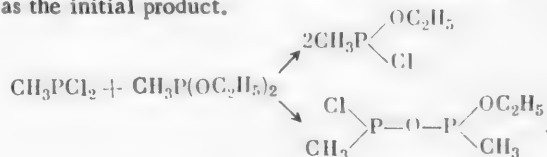
We had shown previously that mixed anhydrides of carboxylic acids with acid phosphates and phosphonates are obtained readily and in quantitative yields by the reaction of silver salts of carboxylic acids with chlorophosphates and chlorophosphonates [1]. The present work is devoted to the synthesis of mixed anhydrides - dialkyl acyl phosphites and alkyl acyl phosphonites - formed from carboxylic acid, dialkyl phosphite and alkyl phosphonite groups. Dialkyl acyl phosphites are substances which are rather difficultly accessible and, in contrast with the dialkyl acyl phosphates, have been little studied; alkyl acyl phosphonites up to the present have not been reported in the literature. Synthesis of the dialkyl acyl phosphites was accomplished previously by the interaction of esters of pyrophosphorous acid with carboxylic acids [2]. However, this method of synthesis is not universal: Some dialkyl acyl phosphites cannot be obtained in the individual form by this scheme, owing to the closeness of the boiling points of the initial and final substances [2, 3]. Another shortcoming of the method is the difficult accessibility of the initial esters of pyrophosphorous acid.

Dialkyl acyl phosphites were obtained in the present work by the action of dialkyl chlorophosphites on salts of carboxylic acids.

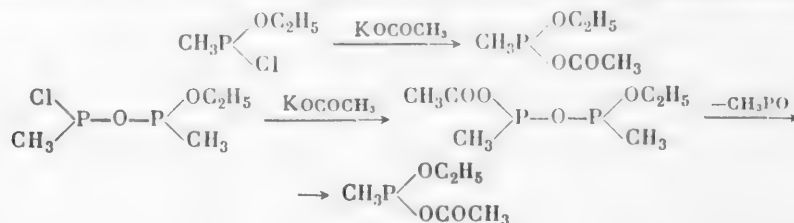


In the instance of preparing diethyl acetyl phosphite, it was established that the nature of the cation in the salts used (Ag, Na, K, Pb) has little influence on the yield of mixed anhydrides, and the most suitable solvent is absolute diethyl ether; the reaction time is varied, depending on the reactants used, from 4 to 10 hours.

It was proposed to obtain the alkyl acyl phosphonites by the reaction of alkyl chlorophosphonites with salts of carboxylic acids. However, the initial acid chlorides [chlorophosphonites] have not been reported in the literature. These compounds are obtained neither by reaction of dichlorophosphonites with one mole of alcohol in the presence of tertiary amines, nor by the interaction of alkyl dichlorophosphonites [alkyl dichlorophosphines] with dialkyl phosphonites. On mixing equimolar quantities of methyl dichlorophosphine with the diethyl ester of methylphosphonous acid, instead of the expected product, ethyl chloride was recovered on distillation. It may be assumed that one or two unstable substances are formed as the initial product.



These compounds give alkyl acyl methylphosphonites on interaction with a potassium carboxylate.



The experiments which were conducted confirmed our surmise: Ethyl acetyl methylphosphonite was obtained successfully by this method, with satisfactory yield.

Dialkyl acyl phosphites and alkyl acetyl phosphonites, in contrast to the corresponding pentavalent compounds, are relatively thermally stable. They distill under vacuum without decomposition, whereas dialkyl acyl phosphates and phosphonates are decomposed with the formation of anhydrides of carboxylic acids, pyrophosphates, or pyrophosphonates [1].

Dialkyl acyl phosphites are readily oxidized by oxides of nitrogen to dialkyl acyl phosphates, which on heating are converted to pyrophosphates.



By the action of alcohols on dialkyl acyl phosphites, trialkyl phosphites and carboxylic acids are obtained.\* On the basis of a study of the properties of dialkyl acyl phosphites conducted by ourselves and other investigators, it may be concluded that these compounds have a resemblance not so much to acid anhydrides as to neutral phosphites, and their properties are determined mainly by the presence of the coordination-unsaturated phosphorus atom in their molecule.

The alcoholysis of dialkyl acyl phosphites evidently will be represented correctly not as the usual type of acylation (with attack by a positively charged particle), but as a reaction of the transesterification type [4].



Attempts to acylate mercaptans and amines by dialkyl acyl phosphites at present have not led to favorable results.

#### EXPERIMENTAL

**Preparation of Dialkyl Acyl Phosphites.** A three-necked flask with stirrer, dropping funnel and reflux condenser was charged with 0.11 mole of anhydrous carboxylate salt and 50 ml of absolute ether. While mixing and boiling gently, 0.1 mole of the dialkyl chlorophosphite was added dropwise over 20–25 minutes, and the reaction mixture was stirred at 35–40° for 5–10 hours more (as long as the chloride ion was detected in the organic phase of the mixture). The precipitate was separated and the ether was distilled off. The residue was vacuum distilled. The operations were carried out in an atmosphere of dry nitrogen. The yields and properties of the compounds obtained are summarized in the table.

**Preparation of Ethyl Acetyl Methylphosphonite.** The apparatus described above was charged with 6.8 g of diethyl methylphosphonite and 50 ml of absolute ether. With mixing and cooling to -10°, 7 g of methyldichlorophosphine was added dropwise to the mixture, and then 11.9 g of anhydrous potassium acetate. The mixture was held at -10° for 1 hour, then 2 hours at 20° and 3 hours with gentle boiling. The precipitate was filtered off, the ether was distilled. The operations were conducted in an atmosphere of dry nitrogen. Obtained 4.85 g (27%) of ethyl acetyl methylphosphonite.

B. p. 89–91 (11 mm),  $n_D^{20}$  1.4320,  $d_4^{20}$  1.0970,  $M_R$  35.47; calculated 34.70.  
Found %: C 40.21, 40.18; H 7.21, 7.39.  $\text{C}_5\text{H}_{11}\text{O}_3\text{P}$ . Calculated %: C 40.00; H 7.35.

**Interaction of Diethyl Acetyl Phosphite with Ethanol.** A mixture of 9 g of diethyl acetyl phosphite and 2.3 g of anhydrous alcohol was heated 6 hours at 80°. After distillation, there was obtained 2.5 g (30%) of triethyl phosphite with b.p. 157–158.5°. The salt with cuprous iodide melted at 106–108°; a mixed sample with a known sample of the salt did not give any melting point depression.

**Oxidation of Diethyl Propionyl Phosphite.** A flask with a calcium chloride drying tube and gas introduction tube was charged with 7g of diethyl propionyl phosphite, and a stream of dry nitrogen in mixture with oxides of nitrogen [5] was passed through the liquid for 2 hours at 0°. The mixture was held under vacuum and heated one

\* A. E. Arbuzov and P. I. Alimov [2] demonstrated that diethyl benzoyl phosphite reacts with ethanol with the formation of triethyl phosphite and benzoic acid. These same authors showed that dialkyl acyl phosphites readily add sulfur and enter into the Arbuzov reaction.

# Synthesis of Dialkyl Acyl Phosphites (RO)<sub>2</sub>POCOR<sup>\*</sup>

R	R'	B.p. (pressure in mm)	n <sub>D</sub> <sup>20</sup>	d <sub>4</sub> <sup>20</sup>	MR <sub>D</sub>		% P		Yield, %
					calc.	found	calc.	found	
C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	67-69 <sup>(9)</sup>	1.4207	1.0710	42.90	42.61	17.25	17.16, 17.07 <sup>*</sup>	65.5
C <sub>3</sub> H <sub>7</sub>	CH <sub>3</sub>	88-89 (6)	1.4234	0.9945	52.22	53.35	14.89	14.39, 14.79	52
C <sub>4</sub> H <sub>9</sub>	CH <sub>3</sub>	110-111 (8)	1.4277	0.9796	61.46	61.99	13.12	12.97, 12.85	61
C <sub>6</sub> H <sub>13</sub>	CH <sub>3</sub>	154-155 (6)	1.4341	0.9422	79.93	80.77	10.50	10.31, 10.39	65
C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	184-185 (1.5)	1.5691	1.1967	72.73	75.58	11.12	10.97, 10.52	55.6
CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	90-93 (10-4)	1.5491	1.1444	81.91	84.43	10.10	9.80, 10.30	53
C <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub> <sup>**</sup>	113-115 (0.5)	1.4962	1.1220	62.48	63.25	12.03	12.42, 12.44	60
C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	80-84 (10-12)	1.4250	1.0450	47.60	47.24	15.92	15.81, 15.85	62

<sup>\*</sup> Found %: C 40.26, 40.18; H 7.67, 7.54. Calculated %: C 40.00; H 7.23.

<sup>\*\*</sup> Literature data [2]: b.p. 102-103° (1 mm), n<sub>D</sub><sup>20</sup> 1.4974, d<sub>4</sub><sup>20</sup> 1.1193.

hour on a water bath to remove the excess oxides. On distillation, there was recovered the anhydride of propionic acid with b.p. 60-62° (20 mm), n<sub>D</sub><sup>20</sup> 1.0131, and tetraethyl pyrophosphate, with b.p. 142-144° (3 mm), n<sub>D</sub><sup>20</sup> 1.4236.

Literature data for propionic anhydride [6]: b.p. 67.5° (18 mm), n<sub>D</sub><sup>20</sup> 1.0120; for tetraethyl pyrophosphate [1]: b.p. 144-145° (3 mm), n<sub>D</sub><sup>20</sup> 1.4225.

**Dihexyl Chlorophosphite.** A flask with stirrer, reflux condenser with calcium chloride drying tube and dropping funnel was charged with 101.5 g of hexyl dichlorophosphite, 75 g of diethylaniline and 500 ml of absolute ether, and 59.1 g of hexanol was added dropwise, cooling with ice. Then the mixture was heated 2 hours on a water bath; the precipitate was filtered off, washed with 100 ml of absolute ether, and pressed. The solvent was distilled off and the residue was vacuum distilled, collecting the fraction with b.p. 145-147° (8 mm). Yield 62 g (46.3%).

n<sub>D</sub><sup>20</sup> 1.4435, d<sub>4</sub><sup>20</sup> 0.9688, MR<sub>D</sub> 73.6; calculated 73.91.

Found %: Cl 13.15, 13.25. C<sub>12</sub>H<sub>26</sub>O<sub>2</sub>PCl. Calculated %: Cl 13.33.

Mobile colorless liquid, fuming in air. It is miscible with the majority of organic solvents; with water it reacts very violently.

**Di-p-tolyl Chlorophosphite.** The apparatus described above was charged with 216.26 g of p-cresol, and 137.5 g of phosphorus trichloride was added dropwise, cooling with ice. Then the mixture was heated 2 hours on a water bath and distilled. Obtained 225 g (80%).

B. p. 161-164° (1 mm), n<sub>D</sub><sup>20</sup> 1.5684, d<sub>4</sub><sup>20</sup> 1.1994, MR<sub>D</sub> 76.60; calculated 76.31.

Found %: Cl 12.50, 12.55. C<sub>14</sub>H<sub>14</sub>O<sub>2</sub>PCl. Calculated %: Cl 12.62.

Oily liquid, miscible with the usual organic solvents, reacting violently with water.

## SUMMARY

The interaction of dialkyl and diaryl chlorophosphites with salts of carboxylic acids leads to various dialkyl acyl phosphites and diaryl acyl phosphites. Ethyl acetyl methylphosphonite has been obtained by the interaction of ethyl chloro (methylphosphonite) with potassium acetate.

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# SYNTHESIS OF ESTERS OF PHOSPHOROUS, PHOSPHONOUS AND PHOSPHINOUS ACIDS BY ALCOHOLYSIS OF THEIR AMIDES

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and V. P. Evdakov

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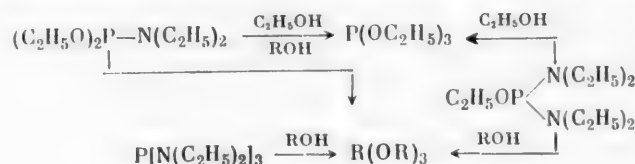
Original article submitted July 22, 1960

For introducing into an alcohol molecule the phosphorous, phosphonous, or phosphinous acid group in place of the hydroxyl hydrogen atom, use is made of the interaction of alcohols (or their alcoholates) with acid chlorides of trivalent phosphorus [1, 2], with mixed anhydrides of phosphoric acid with other acids [3-5], with phosphorous acid [6], and also by transesterification of phosphites and phosphonites [7, 8]. We studied the latter reaction in the instances of transesterification of acid (monoalkyl) esters and neutral (dialkyl and diaryl) esters of phosphonous acids by monobasic and dibasic alcohols; this reaction was found to be a convenient method for synthesizing the corresponding phosphonites. The search for new methods of synthesizing esters of acids of trivalent phosphorus which would proceed under relatively mild conditions and would not be accompanied by the evolution of aggressive materials is currently acquiring great importance in connection with the study of complex phosphites, for example, phosphites of nucleosides [9].

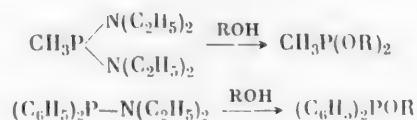
In the present investigation a new method has been developed for preparing phosphites, phosphonites and phosphinites by the alcoholysis of amides. It has been found that by such a method it is possible to prepare various esters of acids of trivalent phosphorus with good yields, with the formation of amines as byproducts which are readily separable from the reaction mixtures. The reaction was studied in the instance of alcoholysis of diethylamides of phosphorous, phosphonous and phosphinous acids by monobasic alcohols.

The monoethylamide of diethyl phosphite is converted to triethyl phosphite by the action of ethyl alcohol with heating on a water bath. If the reaction is conducted with higher alcohols taken in excess, there occurs (along with alcoholysis of the amide group) transesterification and the formation of the corresponding neutral phosphite.

The di-diethylamide [tetraethyldiamide] of monoethyl phosphite also reacts analogously with alcohol; On using ethyl alcohol, triethyl phosphite is formed, and on using higher alcohols (taken in excess), the corresponding trialkyl phosphites are formed. Similarly to the amido esters of phosphorous acid, the tri-diethylamide [hexaethyl-triamide] of phosphorous acid also undergoes alcoholysis, the neutral phosphite being formed.

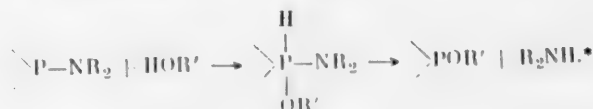


The alcoholysis of diethylamides of phosphonous acids, similarly to that described above, leads to the corresponding phosphonites.



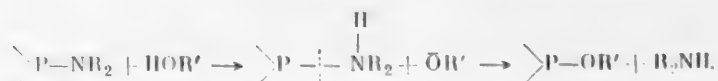
The full amides of acids of trivalent phosphorous enter into reaction not only with alcohols, but also with phenols, the corresponding phenyl esters being formed with good yields.

The alcoholysis of amides may be represented by analogy with the transesterification of esters of acids of trivalent phosphorous as a process taking place through a stage of formation of an unstable addition product with pentavalent phosphorous, of the type of a phosphonium compound:



The heterolytic splitting of the P-N bond and the formation of the amine and ether possibly precedes the formation of a hydrogen bond between the hydrogen atom (connected with the phosphorous) and the nitrogen, which favors a significant polarization of the phosphorus-nitrogen bond.

It is also possible that the first act of the alcoholysis is addition of the proton to the nitrogen atom; the P-N bond is polar, the nitrogen being the negative end of the dipole (the electronegativity of nitrogen, according to Pauling, is 3.0, and phosphorus 2.1 eV). In the unstable intermediate product thus formed, there occurs heterolytic rupture of the phosphorus-nitrogen bond and addition of the alkoxyl anion to the phosphorus:



These surmises are confirmed by the fact that the diethylamide of diethyl phosphite is not subject to alcoholysis under analogous conditions.

The diethylamides of acids of trivalent phosphorus, including some not previously described in the literature, were prepared by the interaction of the corresponding acid chlorides with diethylamine.

#### EXPERIMENTAL

**Diethylamide of Diethyl Phosphite.** A four-necked flask with stirrer, reflux condenser, thermometer and dropping funnel was charged with 34 g of anhydrous ethanol, 74.2 g of triethylamine and 300 ml of absolute ether. With vigorous stirring and cooling to 0°, there was added dropwise 58 g of the dichloroanhydride of diethylamidophosphorous acid [Cl<sub>2</sub>PNEt<sub>2</sub>] in 50 ml of absolute ether; the temperature of the mixture should not exceed 10°; the mixture was stirred for 6 hours more at room temperature and allowed to stand overnight. The precipitate was separated, the solvent was distilled off, and the residue was vacuum distilled. Yield 49.5 g (60%).

B. p. 55–56° (80 mm),  $n_D^{20}$  1.4318,  $d_4^{20}$  0.9190,  $M_R$  54.46; calculated 55.10.

Found %: N 7.19, 7.16. C<sub>8</sub>H<sub>20</sub>NP. Calculated %: N 7.25.

Colorless oil with sharp odor, soluble in the usual organic solvents, insoluble in water.

**Tetraethyldiamide of Methylphosphonous Acid.** As described above, to 87.5 g of diethylamine in 100 ml of absolute ether, with mixing and cooling to 0°, there was added dropwise 35 g of methyldichlorophosphine in 60 ml of absolute ether, the mixture was stirred 1 hour more with heating in a water bath, the precipitate was separated, the solvent was evaporated, and the remaining oil was vacuum distilled. All operations should be carried out in a dry nitrogen atmosphere. Obtained 20 g (37%); b.p. 82–85° (11 mm),  $n_D^{20}$  1.4658,  $d_4^{20}$  0.8990.

Found %: N 14.75, 14.68. C<sub>9</sub>H<sub>23</sub>N<sub>2</sub>P. Calculated %: N 14.72.

Colorless oil with sharp odor, soluble in organic solvents, insoluble in water.

\* The addition of the proton to the phosphorous and not to the nitrogen may sometimes be preferred, owing to the greater shielding of the nitrogen atom. For this reason, triphenylphosphine is a stronger base than triphenylamine [10].

Diethylamide of Diphenylphosphinous Acid. As described above, from 10 g of diethylamine (in 50 ml of absolute ether) and 14.8 g of diphenylchlorophosphine; obtained 11.4 g (65%).

B.p. 140–142° (0.7 mm),  $n_D^{20}$  1.5908,  $d_4^{20}$  1.0430.

Found %: N 5.55, 5.6; P 12.15, 12.20.  $C_{16}H_{20}NP$ . Calculated %: N 5.45; P 12.05.

Thick liquid, light yellow color, soluble in organic solvents, insoluble in water.

Alcoholysis of Hexaethyltriamide of Phosphorous Acid.

a) By Ethanol. A flask with a reflux condenser was charged with 7 g of the triamide and 7.8 g of anhydrous alcohol, and the mixture was heated in an inert gas atmosphere in a water bath for 20 hours. After distilling, obtained: 3.8 g (79%) triethyl phosphite with b.p. 62–67° (25 mm),  $n_D^{20}$  1.4080 and 8.3 g diethylamine with b.p. 57–58°,  $n_D^{20}$  1.3844.

Literature data: triethyl phosphite [2], b.p. 62–65° (24 mm),  $n_D^{20}$  1.4101; diethylamine [11], b.p. 58°,  $n_D^{20}$  1.3871.

b) By n-Amyl Alcohol. As described above, from 10.9 g of the triamide and 23.4 g of amyl alcohol; obtained 8.8 g (68%) triamyl phosphite with b.p. 126–127° (8 mm),  $n_D^{20}$  1.4303,  $d_4^{20}$  0.9170.

Found %: P 10.63, 10.99.  $C_{15}H_{33}O_3P$ . Calculated %: P 10.63.

Literature data [12]: b.p. 102° (0.25 mm),  $n_D^{20}$  1.4370.

c) By 2-Ethylhexanol. As described above, from 8.5 g of the triamide and 27 g of 2-ethylhexanol; obtained 10.5 g (83%) tri-(2-ethylhexyl) phosphite with b.p. 155–156° (1 mm),  $n_D^{20}$  1.4476,  $d_4^{20}$  0.9114.

Found %: P 7.56, 7.62.  $C_{24}H_{51}O_3P$ . Calculated %: P 7.42.

Colorless oil, miscible with organic solvents, insoluble in water.

Alcoholysis of Tetraethyldiamide of Monoethyl Phosphite.

a) By Ethanol. As described above, but with 10 hours heating in a water bath, from 12 g of the diamide and 10 g of anhydrous ethanol; obtained 9.15 g (74.5%) triethyl phosphite with b.p. 60–62° (22 mm),  $n_D^{20}$  1.4123.

b) By 2-Ethylhexanol. As described above, from 6.3 g of the diamide and 22 g of 2-ethylhexanol; obtained 6 g of tri-(2-ethylhexyl) phosphite with b.p. 155–156° (1 mm),  $n_D^{20}$  1.4471.

Alcoholysis of Diethylamide of Diethyl Phosphite.

a) By Ethanol. As described above, but with 4 hour heating in a water bath, from 6.0 g of the diethylamide and 4.3 g of anhydrous alcohol; obtained 3.4 g (70%) triethyl phosphite with b.p. 54–55° (17 mm),  $n_D^{20}$  1.4100.

b) By n-Hexanol. As described above, but with 4 hour heating in an oil bath at 150–170°, from 5.8 of the diethylamide and 9.1 g of n-hexanol; obtained 6.7 g (67%) trihexyl phosphite.

B.p. 138–139° (1 mm),  $n_D^{20}$  1.4419.

Found %: P 9.30, 9.21.  $C_{18}H_{39}O_3P$ . Calculated %: P 9.28.

Literature data [13]: b.p. 167–178° (3 mm),  $n_D^{20}$  1.4428.

c) By 2-Ethylhexanol. As described above, but with 20 hour heating in a water bath, from 3.9 g of the diethylamide and 15.7 g of 2-ethylhexanol; obtained 3.5 g (45%) tri-(2-ethylhexyl) phosphite with b.p. 155–156° (1 mm),  $n_D^{20}$  1.4471.

Alcoholysis of Tetraethyldiamide of Methylphosphonous Acid.

a) By 2-Ethylhexanol. As described above, from 5.4 g of the diamide and 14.75 g of 2-ethylhexanol; obtained 3.1 g (35%) di(2-ethylhexyl) methylphosphonite.

B.p. 150–152° (0.7 mm),  $n_D^{20}$  1.4365,  $d_4^{20}$  0.9142.

Found %: P 9.71.  $C_{17}H_{37}O_2P$ . Calculated %: P 11.20.

Colorless liquid, readily soluble in organic solvents, readily oxidized in air.

b) By Phenol. As described above, from 4.4 g of the diamide and 8.7 g of phenol; obtained 2.7 g (56%) diphenyl methylphosphonite with b.p. 144–148° (9 mm),  $n_D^{20}$  1.5560,  $d_4^{20}$  1.1420.

Found %: P 13.42, 13.45.  $C_{13}H_{13}O_2P$ . Calculated %: P 13.35.

Colorless liquid, readily soluble in organic solvents.



Alcoholysis of Diethylamide of Diphenylphosphinous Acid. As described above, from 2.5 g of the diethylamide of diphenylphosphinous acid and 2 ml of anhydrous alcohol; obtained 1.2 g (50%) ethyl diphenylphosphinite with b.p. 127–128° (1 mm),  $n_D^{20}$  1.5910. On isomerizing the obtained phosphinite with ethyl iodide by the method of A. E. Arbuzov [14], obtained phenyldiethylphosphine oxide with m.p. 121–123°; a mixed sample with a known sample of phenyldiethylphosphine oxide did not give any melting point depression.

#### SUMMARY

The alcoholysis of diethylamides of acids of trivalent phosphorus is a new method for the synthesis of neutral phosphites, phosphonites and phosphinites. A mechanism is proposed for the alcoholysis.

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# N-CARBETHOXYARENEIMINOSULFONYL CHLORIDES

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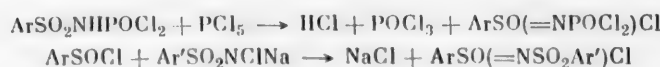
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N-dichlorophosphinylareneiminosulfonyl chlorides were prepared recently by reacting phosphorus pentachloride with diacyl chlorides of N-arylsulfonylamidophosphoric acids [1], and N-arylsulfonylareneiminosulfonyl chlorides were obtained by reacting sodium salts of arenesulfonylchloramides with arenesulfinyl chlorides [2].



Both types of acyl chlorides are starting materials for the preparation of a wide variety of iminosulfonic acid derivatives substituted at the nitrogen atom attached to the phosphinyl or arylsulfonyl group [1-3], but it is doubtful if these could be used to prepare derivatives of iminosulfonic acid derivatives with free imino groups, which is of considerable theoretical interest. In order to obtain such derivatives it is evidently necessary to start with compounds containing on the nitrogen atom a group which subsequently may be removed readily. The carbamido and carbalkoxy groups may be used for this purpose. Therefore, it was decided to try to prepare iminosulfonic acid derivatives starting with the corresponding compounds, particularly the sodium salts of esters of N-chlorocarbamic acids.

When the sodium salt of ethyl N-chlorocarbamate was reacted with arenesulfinyl chlorides, yields of 90 - 95% were obtained of the N-carbethoxyareneiminosulfonyl chlorides (Table 1), which are viscous, almost colorless liquids or low-melting crystalline compounds with a faint odor resembling that of arenesulfonyl chlorides, insoluble in water, very slightly soluble in petroleum ether, very soluble in benzene, ether, methanol, ethanol and carbon tetrachloride (exceptions are shown in Table 1).



The liquid acyl chlorides were purified by vacuum distillation, while the crystalline ones were washed or recrystallized. The N-carbethoxyareneiminosulfonyl chlorides were hydrolyzed very slowly by water at 20°, and they reacted slowly with boiling alcohol, while the crystalline compounds were recrystallized easily from methanol with negligible losses. The N-carbethoxyareneiminosulfonyl chlorides reacted very readily with ammonia, amines, phenolates and alcoholates, forming the corresponding derivatives.

Determination of the specific gravity and index of refraction of the liquid N-carbethoxyareneiminosulfonyl chlorides enabled the refraction of the SO(=N-)Cl group (Table 2) to be calculated.

When boiled with a 2 N aqueous solution of potassium hydroxide, N-carbethoxyareneiminosulfonyl chlorides hydrolyzed, forming N-carbethoxyarenesulfonamides:



and this fact in combination with the analytical data and the method of preparation is sufficient to prove the structure of N-carbethoxyareneiminosulfonyl chlorides.

N-Carbethoxyarenesulfonamides (Table 3) are comparatively low-melting crystalline, colorless compounds, very soluble in benzene, ether and alcohol, and somewhat soluble in water and petroleum ether. They all crystal-

TABLE 1 N-Carboxyareneiminosulfonyl Chlorides of the Type ArSO( = NCOOC<sub>2</sub>H<sub>5</sub>) Cl

Ar	Yield, %	M. p.	B. p. (pressure in mm)	External form	Formula	Found, %	Calculated, %
C <sub>6</sub> H <sub>5</sub>	94	—	147–148° (0.4)	Liquid	C <sub>9</sub> H <sub>10</sub> O <sub>3</sub> NCIS	Cl 14.59, 14.64	Cl 14.31
p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	90	—	152–153 (0.2)	Liquid	C <sub>10</sub> H <sub>13</sub> O <sub>3</sub> NCIS	Cl 13.45, 13.40	Cl 13.54
p-ClC <sub>6</sub> H <sub>4</sub>	89	54–56°	—	Colorless prisms•	C <sub>10</sub> H <sub>12</sub> O <sub>3</sub> NCIS	Cl 15.50, 12.57	Cl 12.76
p-BrC <sub>6</sub> H <sub>4</sub>	98	—	153–154 (0.2)	Liquid	C <sub>9</sub> H <sub>9</sub> O <sub>3</sub> NCIS	Cl 24.55, 24.64	Cl 25.13
o-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	96	—	168–169 (0.3)	Viscous liquid	C <sub>9</sub> H <sub>9</sub> O <sub>3</sub> NCIBrS	Cl+Br 34.85, 34.84	Cl+Br 35.32
	90	73–75	—	Colorless prisms••	C <sub>9</sub> H <sub>9</sub> O <sub>3</sub> N <sub>2</sub> ClS	Cl 12.00, 12.06	Cl 12.11
m-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	91	—	—	Light yellow, viscous liquid•••	C <sub>9</sub> H <sub>9</sub> O <sub>3</sub> N <sub>2</sub> ClS	N 9.27, 9.39	N 9.57
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	93	96–98	—	Light yellow needles••	C <sub>9</sub> H <sub>9</sub> O <sub>3</sub> N <sub>2</sub> ClS	Cl 11.48, 11.57	Cl 12.11
β-C <sub>10</sub> H <sub>7</sub>	95	66–67	—	Light yellow prisms•	C <sub>13</sub> H <sub>12</sub> O <sub>3</sub> NCIS	Cl 12.31, 12.33	Cl 12.11
						N 9.34, 9.20	N 9.57
						Cl 11.78, 11.76	Cl 11.91

• Washed with a small quantity of methanol.

•• Slightly soluble at 20°, readily soluble in boiling methanol, ethanol, and carbon tetrachloride. Recrystallized from methanol or carbon tetrachloride.

••• Purified by reprecipitation with petroleum ether from a benzene solution.

lize slowly and with difficulty. We were unable to prepare N-carbethoxybenzenesulfonamide in the crystalline state, although in the literature it is described as a crystalline substance with m.p. 109° [4]. The N-carbethoxynitrobenzenesulfonamides were identical with those described in the literature [5]. The N-carbethoxyarenesulfonamides are acidic in nature and dissolve readily in aqueous solutions of alkali bicarbonates, carbonates and hydroxides, forming salts. When these alkaline solutions are acidified the N-carbethoxyarenesulfonamides are precipitates in their original form.

TABLE 2  
Specific Gravity and Refraction of Liquid N-Carbethoxyarene-  
iminosulfonyl Chlorides of the Type  $\text{ArSO}(=\text{NCOOC}_2\text{H}_5)\text{Cl}$

Ar	$d_4^{20}$	$n_D^{20}$	$MR_D$	$MR_D$ for the -SO(=N-)Cl group
$\text{C}_6\text{H}_5$	1.3270	1.5600	60.36	18.54
p- $\text{CH}_3\text{C}_6\text{H}_4$	1.2917	1.5600	65.50	19.07
p- $\text{ClC}_6\text{H}_4$	1.4126	1.5720	65.72	19.04
p- $\text{BrC}_6\text{H}_4$	1.6090	1.5911	68.62	19.04
			Average	18.92

The sodium salt of ethyl N-chlorocarbamate was prepared by a method somewhat different from that described in the literature [6] (see EXPERIMENTAL).

#### EXPERIMENTAL

**N-Carbethoxyareneiminosulfonyl Chlorides (Table 1).** To a vigorously stirred suspension of 0.11 g-mole of the sodium salt of ethyl N-chlorocarbamate in 70 ml of dry benzene was added a solution of 0.1 g-mole of an arenesulfinyl chloride in 50 ml of benzene at a rate such that the temperature of the reaction mixture did not exceed 40–45°. The reaction mixture was then heated for 30–40 minutes at 60–65°. After cooling, the sodium chloride was filtered off with suction, the benzene distilled off under vacuum, and the residue fractionally distilled or recrystallized.

**Ethyl N-Chlorocarbamate.** One g-mole of ethyl carbamate was dissolved in 300 ml of water and chlorine was passed in at a rate such that the temperature did not rise above 20°. Completion of the reaction was determined by the increase in weight. When the chlorination was finished an oily layer separated which was washed with water and distilled; b.p. 102–103° (30 mm), yield 65% (cf. [7]).

**Sodium Salt of Ethyl N-Chlorocarbamate.** A solution of 0.6 g-mole of sodium methylate in 200 ml of methanol was stirred vigorously at 15–20° and cooled with ice water while 0.6 g-mole of ethyl N-chlorocarbamate was added during 40–60 minutes. About two-thirds of the methanol was distilled off under vacuum at 40–45°. To the residue was added dry ether (300–400 ml); the precipitated sodium salt was filtered off rapidly with suction and dried for two to three hours under vacuum at 50°. Yield about 70% (cf. [6]).

**N-Carbethoxyarenesulfonamides (Table 3).** A mixture of 0.01 g-mole of an N-carbethoxyareneiminosulfonyl chloride and 10 ml of 2 N potassium hydroxide was heated on a steam bath until the acid chloride was completely dissolved (30–40 minutes). The solution was cooled to 0° and carefully acidified with 5 N hydrochloric acid until acid to Congo red. The N-carbethoxyarenesulfonamides separated in the form of an oil which gradually solidified. They were purified by reprecipitation from a solution of sodium bicarbonate with hydrochloric acid, and then crystallized from a suitable solvent.

#### SUMMARY

1) N-Carbethoxyareneiminosulfonyl chlorides were prepared by reacting the sodium salt of ethyl N-chlorocarbamate with arenesulfonyl chlorides.

TABLE 3 N-Carboethoxyarenesulfonamides of the Type  $\text{ArSO}_2\text{NHCOOC}_2\text{H}_5$  Prepared by Hydrolysis of N-Carboethoxyareneiminosulfonyl Chlorides

Ar	Yield, %	M. p.	External form; solvent used in crystallization	Formula	Found, %	Calculated, %
$\text{C}_6\text{H}_5$	83	—	Viscous, colorless liquid [4]*	$\text{C}_9\text{H}_{11}\text{O}_4\text{NS}$	S 13.60, 13.58	S 13.98
p- $\text{CH}_3\text{C}_6\text{H}_4$	96	75—77°	Fine crystalline powder	$\text{C}_{10}\text{H}_{13}\text{O}_4\text{NS}$	S 13.55, 13.57	S 13.18
p- $\text{CH}_3\text{OC}_6\text{H}_4$	65	114—116	Prisms; water + alcohol, then benzene	$\text{C}_{10}\text{H}_{13}\text{O}_5\text{NS}$	S 12.10, 12.16	S 12.36
p- $\text{ClC}_6\text{H}_4$	73	90—92	Prisms; benzene + petroleum ether	$\text{C}_9\text{H}_{10}\text{O}_4\text{NCIS}$	Cl 13.70, 13.70	Cl 13.44
p- $\text{BrC}_6\text{H}_4$	67	85—87	Prisms; benzene + petroleum ether	$\text{C}_9\text{H}_{10}\text{O}_4\text{NBrS}$	Br 25.81, 26.25	Br 25.93
o- $\text{NO}_2\text{C}_6\text{H}_4$	90	153—155	Prisms; ethanol	$\text{C}_9\text{H}_{10}\text{O}_6\text{N}_2\text{S}$	[5]	—
p- $\text{NO}_2\text{C}_6\text{H}_4$	79	102—103	Prisms; methanol + water, then benzene	$\text{C}_9\text{H}_{10}\text{O}_6\text{N}_2\text{S}$	[5]	—
p- $\text{NO}_2\text{C}_6\text{H}_4$	93	132—134	Needles; water, then benzene	$\text{C}_9\text{H}_{10}\text{O}_6\text{N}_2\text{S}$	[5]	—
$\beta\text{-C}_{10}\text{H}_7$	79	86—88	Needles; benzene + petroleum ether	$\text{C}_{13}\text{H}_{13}\text{O}_4\text{NS}$	S 11.01, 11.25	S 11.48

\* Prepared also by reacting ethyl chlorocarbonate with benzenesulfonamide (cf [5]), and by reacting ethanol with phenylsulfonylisocyanate [4]. In all cases the N-carboethoxybenzenesulfonamide was obtained in the form of a viscous liquid.

2) N-Carbethoxyarenesulfonamides were prepared by alkaline hydrolysis of N-carbethoxyareneiminosulfonyl chlorides.

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# TRIARYLOXYPHOSHAZO-N-ARYLSULFONYLIMINOBENZOYLS AND N-DIARYLOXYPHOSPHINYL-N'-ARYLSULFONYLBENZAMIDINES

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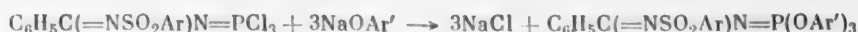
pp. 2385-2390, July, 1961

Original article submitted July 25, 1960

In a previous paper [1] it was shown that trichlorophosphazo-N-arylsulfonyliminobenzoyls are formed by reacting phosphorus pentachloride with N-arylsulfonylbenzamidines.



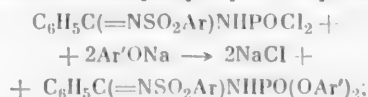
In their chemical properties trichlorophosphazo-N-arylsulfonyliminobenzoyls resemble trichlorophosphazoacyls [2]. They react with sodium arylates in dioxane or benzene solutions to give triaryloxyphosphazo-N-arylsulfonyliminobenzoyls.



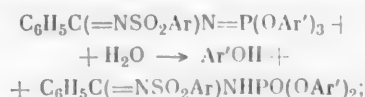
The latter are almost colorless, very viscous liquids or comparatively low-melting substances (Table 1) of a neutral nature. They are very similar chemically to triaryloxyphosphazoacyls [3]. Like the latter they are hydrolyzed very readily, being transformed into N-diaryloxyphosphinyl-N'-arylsulfonylbenzamidines, which are comparatively stable as regards further hydrolysis (see below). Hydrolysis takes place almost quantitatively upon standing with water, or by boiling for a short time with water or water-alcohol solutions, and even by the action of moisture in the air. Therefore, in experiments with triaryloxyphosphazo-N-arylsulfonyliminobenzoyls, contact with moisture of the air must be avoided.

N-Diaryloxyphosphinyl-N'-arylsulfonylbenzamidines, being N-sulfonylimino derivatives of diesters of arylsulfonylamidophosphoric acids, may be prepared by three methods:

- 1) by reacting sodium arylates with N-dichlorophosphinyl-N'-arylsulfonylbenzamidines:



- 2) by hydrolyzing triaryloxyphosphazo-N-arylsulfonyliminobenzoyls (see above):



- 3) by reacting acid chlorides of N-diaryloxyphosphinyliminocarboxylic acids with amides of arenesulfonic acids in the presence of triethylamine:

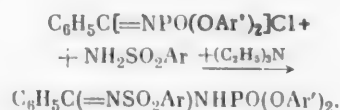


TABLE 1

Triaryloxyphosphazo-N-arylsulfonyliminobenzoyls of the Type  $C_6H_5C(=NSO_2Ar)N=P(OAr')_3$  •

Ar	Ar'	Yield, %	M. p.	External form; solvent used in crystallization	Found, %	Formula	Calculated, %
$C_6H_5$ $C_6H_5$ $p-ClC_6H_4$	$C_6H_5$ $p-ClC_6H_4$ $C_6H_5$	63 84 78	— — 127—129°	Liquid •• Liquid •• Prisms; benzene + petroleum ether	N 4.07, 4.02 Cl 16.15, 16.04 N 4.67, 4.63	$C_{31}H_{25}O_5N_2SP$ $C_{31}H_{23}O_5N_2Cl_2SP$ $C_{32}H_{27}O_5N_2SP$	N 3.64 Cl 15.83 N 4.81
$p-CH_3C_6H_4$ $p-NO_2C_6H_4$	$p-ClC_6H_4$ $C_6H_5$	85 77	— 129—131	Liquid •• Prisms; benzene + petroleum ether	Cl 15.03, 14.97 N 6.88, 6.79	$C_{32}H_{24}O_5N_2Cl_2SP$ $C_{31}H_{24}O_5N_2SP$	Cl 15.51 N 6.84
$p-NO_2C_6H_4$ $p-ClC_6H_4$	$p-ClC_6H_4$ $C_6H_5$	95 83	— 114—117	Liquid •• Prisms; benzene + petroleum ether	Cl 14.20, 14.34 N 4.40, 4.48	$C_{31}H_{21}O_5N_2Cl_2SP$ $C_{31}H_{24}O_5N_2Cl_2SP$	Cl 14.85 N 4.64

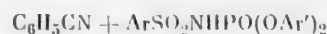
• All these compounds were quite soluble in benzene and dioxane, but sparingly soluble in petroleum ether.

•• Purified by fractional precipitation from benzene with petroleum ether.

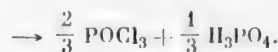
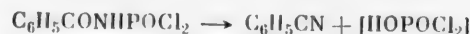
N-Diaryloxyphosphinyl-N'-arylsulfonylbenzamidines are most conveniently prepared by reacting trichlorophosphazo-N-arylsulfonyliminobenzoyls directly with phenols in the presence of tertiary bases (pyridine, triethylamine), with subsequent treatment of the reaction mixture with water and without separation of the triaryloxyphosphazo-N-arylsulfonyliminobenzoyls.

N-Diaryloxyphosphinyl-N'-arylsulfonylbenzamidines (Table 2) are colorless crystalline substances, insoluble in water and in dilute solutions of acids. They are weak acids and may be titrated like monobasic acids in aqueous or water-alcohol solutions in the presence of phenolphthalein.

When heated at 200–225° in a vacuum (0.1–0.2 mm), N-diaryloxyphosphinyl-N'-arylsulfonylbenzamidines cleave into benzonitriles and the corresponding diesters of arylsulfonylamidophosphoric acids:



This cleavage is similar to the thermal cleavage of trichlorophosphazoacids [2], triaryloxyphosphazoacids [3] and diacyl chlorides of aroylamidophosphoric acids [4]:



## EXPERIMENTAL

Triaryloxyphosphazo-N-arylsulfonyliminobenzoyls (Table 1). A solution of 0.005 g-mole of trichlorophosphazo-N-arylsulfonyliminobenzoyl in 30–50 ml of dioxane was stirred continuously and cooled with ice water while a solution of 0.015 g-mole of sodium arylate in 20–30 ml of dioxane was added to it. The reaction proceeded with a small evolution of heat. After ten minutes the reaction mixture was heated on a steam bath (20–25 minutes), cooled to room temperature, centrifuged, the sodium chloride filtered off, and the dioxane distilled off under vacuum. The residue contained viscous oils or crystalline substances which were purified by recrystallization or reprecipitation.

## N-Diaryloxyphosphinyl-N'-arylsulfonylbenzamidines (Table 2).

A) From Trichlorophosphazo-N-arylsulfonyliminobenzoyls and Phenols in the Presence of Bases. A solution of 0.01 g-mole of trichlorophosphazo-N-arylsulfonyliminobenzoyl in 20 ml of dioxane was stirred continuously and cooled with ice water while a mixture of 0.03 g-mole of phenol, 0.032 g-mole of pyridine (or triethylamine) and 25 ml of dioxane was added gradually to it. The temperature increased as a result of the reaction (40–60°). When all the reactants had been added the mixture was allowed to stand one to one and one-half hours and then 100–150 ml of water was added. An oil separated which slowly crystallized when rubbed with a glass rod. The crystals were filtered with suction, washed with water and alcohol and recrystallized.

B) From Triaryloxyphosphazo-N-arylsulfonyliminobenzoyls by Hydrolysis in Water-Alcohol Solutions. A mixture of 0.01 g-mole of triaryloxyphosphazo-N-arylsulfonyliminobenzoyl and 20 ml of 50% ethanol was refluxed until all the solid was dissolved (20–30 minutes). When the clear solution was cooled, crystals or an oil which soon crystallized separated from it. The substance was filtered with suction, washed with water and alcohol and recrystallized.

C) From N-Dichlorophosphinyl-N'-arylsulfonylbenzamidines and Sodium Arylates. A suspension of 0.01 g-mole of N-dichlorophosphinyl-N'-arylsulfonylbenzamidines in 30 ml of dioxane was stirred continuously and cooled with ice water while a solution of 0.02 g-mole of sodium phenolate in 20 ml of dioxane was added gradually to it (the mixture heated up to 40–50°). After 10–15 minutes the reaction mixture was heated on a steam bath (20–30 minutes), cooled, and diluted with 100–150 ml of water. Crystals or an oil which crystallized slowly when rubbed with a glass rod separated. The crystals were filtered off with suction, washed with water and alcohol and recrystallized.

D) From Acyl Chlorides of N-Diaryloxyphosphinyliminocarboxylic Acids and Arylsulfonamides in the Presence of Triethylamine. To a solution of 0.01 g-mole of N-diaryloxyphosphinyliminobenzoyl chloride in 15–20 ml of chlorobenzene was added 0.01 g-mole of benzenesulfonamide and 0.012 g-mole of triethylamine and the mixture was slowly heated on an oil bath. At 80–100° all the benzenesulfonamide dissolved, and the reaction mixture became completely clear. After five to ten minutes triethylammonium chloride began to precipitate. Soon the reaction mixture was transformed into a solid crystalline mass. After an additional ten minutes the reaction mixture was cooled, the triethylammonium chloride was filtered off with suction, and 15 ml of petroleum ether was added to the filtrate. An oil separated which slowly crystallized upon treatment with hydrochloric acid and rubbing with a glass rod. It was identified by a mixed melting point test.

Thermal Cleavage of N-Diphenoxyphosphinyl-N'-phenylsulfonylbenzamidines. N-Diphenoxyphosphinyl-N'-phenylsulfonylbenzamidines (0.02 g-mole) was placed in a Claisen flask equipped with a capillary and thermometer and connected with a condenser and receiver. Cleavage was effected by heating in an oil bath under a vacuum of 1–0.2 mm. Cleavage began at 175° (in the oil bath) and was accompanied by some tar formation; the benzonitrile formed was distilled off. The temperature of the bath was increased gradually to 200–210°. The diphenyl ester of phenylsulfonylamidophosphoric acid remained in the flask in the form of a thick crystalline mass, dark brown in color owing to the presence of tars. The yield of crude ester was about 100%. After washing with alcohol and recrystallizing from alcohol (activated charcoal) the yield was 74%; m.p. 138–140°; identification by mixed melting point test. Yield of benzonitrile 63%.

The same conditions were used in the thermal cleavage of N-diphenoxyphosphinyl-N'-p-nitrophenylsulfonylbenzamidines [dec. at 200–225°; yield of benzonitrile 46%; yield of diphenyl ester of p-nitrophenylsulfonylamidophosphoric acid (crude) about 100%, recrystallized—72%; identification by mixed melting-point test] and N-diphenoxyphosphinyl-N'-p-tolylsulfonylbenzamidines—dec. at 205–225°, yield of benzonitrile 64%, yield of diphenyl ester of p-tolylsulfonylamidophosphoric acid (crude) 95%, recrystallized—70%. The latter has not been described in the literature and was therefore synthesized by the process we developed previously [5], yield 85%, colorless prisms (from alcohol), m.p. 182–184°, does not give a melting point depression with the compound prepared by thermal cleavage of N-diphenoxyphosphinyl-N'-p-tolylsulfonylbenzamidines.

Found %: N 3.62, 3.58.  $C_{19}H_{18}O_5NSP$ . Calculated %: N 3.47.

## SUMMARY

1. Triaryloxyphosphazo-N-arylsulfonylbenzamidines were prepared by reacting sodium arylates with trichlorophosphazo-N-arylsulfonyliminobenzoyls.

TABLE 2  
N-Diaryloxyphosphinyl-N'-arylsulfonylbenzamidines of the Type  $C_6H_5C(=NSO_2Ar)NHR_1$  (OAr')<sub>2</sub>

Ar	Ar'	Yield, %	M. p.	External form; solvent used in crystallization	Found, %	Formula	Calculated, %	Solubility*			
								benzene	CCl <sub>4</sub>	dioxane	acetone
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	90** 63*** 50*****	153—154°	Prisms; ethanol	N 5.78, 5.80	C <sub>31</sub> H <sub>25</sub> O <sub>3</sub> N <sub>2</sub> SP	N 5.69	+	—	+	+
C <sub>6</sub> H <sub>5</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	63**	143—144	Prisms; ethanol	N 4.96, 4.85 Cl 12.58, 12.68	C <sub>25</sub> H <sub>19</sub> O <sub>3</sub> N <sub>2</sub> Cl <sub>2</sub> P	N 4.99, Cl 12.65	+	+	+	+
p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	86** 47*** 60*****	143—144	Prisms; benzene	N 5.52, 5.50	C <sub>26</sub> H <sub>23</sub> O <sub>3</sub> N <sub>2</sub> SP	N 5.53	+	—	+	+
p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	53**	155—156	Long prisms; ethanol + water	Cl 12.30, 12.28	C <sub>26</sub> H <sub>21</sub> O <sub>3</sub> N <sub>2</sub> Cl <sub>2</sub> SP	Cl 12.32	+	—	+	+
p-ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	79** 98***	154—156	Prisms; ethanol	N 5.57, 5.65	C <sub>25</sub> H <sub>20</sub> O <sub>3</sub> N <sub>2</sub> ClSP	N 5.32	—	—	+	+
p-ClC <sub>6</sub> H <sub>4</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	95**	165—166	Prisms; ethanol	Cl 17.74, 17.64	C <sub>25</sub> H <sub>18</sub> O <sub>3</sub> N <sub>2</sub> Cl <sub>3</sub> SP	Cl 17.84	—	—	+	+
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	95**	181—182	Needles; acetone	N 7.67, 7.67	C <sub>25</sub> H <sub>20</sub> O <sub>7</sub> N <sub>3</sub> SP	N 7.82	—	—	+	+
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	78** 92*****	185—186	Prisms; methanol	N 6.86, 6.71 Cl 11.75, 11.72	C <sub>25</sub> H <sub>18</sub> O <sub>7</sub> N <sub>3</sub> Cl <sub>3</sub> SP	N 6.93, Cl 11.71	—	—	—	—
α-C <sub>10</sub> H <sub>7</sub>	C <sub>6</sub> H <sub>5</sub>	85** 85***	154—156	Prisms; ethanol	N 4.95, 5.10	C <sub>29</sub> H <sub>23</sub> O <sub>3</sub> N <sub>2</sub> SP	N 5.16	—	—	+	+
α-C <sub>10</sub> H <sub>7</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	84**	189—190	Prisms; ethanol	Cl 11.58, 11.49	C <sub>29</sub> H <sub>21</sub> O <sub>3</sub> N <sub>2</sub> Cl <sub>2</sub> SP	Cl 11.60	—	—	+	+
β-C <sub>10</sub> H <sub>7</sub>	C <sub>6</sub> H <sub>5</sub>	85** 45*****	177—180	Prisms; ethanol	N 5.22, 5.23	C <sub>29</sub> H <sub>23</sub> O <sub>3</sub> N <sub>2</sub> SP	N 5.16	—	—	—	—
β-C <sub>10</sub> H <sub>7</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	60**	173—174	Needles; ethanol	Cl 11.60, 11.57	C <sub>29</sub> H <sub>21</sub> O <sub>3</sub> N <sub>2</sub> Cl <sub>2</sub> SP	Cl 11.60	—	—	+	+

\* + Very soluble at the boiling point, — slightly soluble at the boiling point, = insoluble at the boiling point. All substances insoluble in boiling water.

\*\* By method A (see EXPERIMENTAL).

\*\*\* By method B.

\*\*\*\* By method C.

\*\*\*\*\* By method D.

2. N-Diaryloxyphosphinyl-N'-arylsulfonylbenzamidines were prepared by hydrolyzing triaryloxyphosphazo-N-arylsulfonyliminobenzoyls, by reacting sodium arylates (or phenols and bases) with N-dichlorophosphinyl-N'-arylsulfonylbenzamidines, and by reacting acid chlorides of N-diaryloxyphosphinyliminocarboxylic acids with amides of arenesulfonic acids in the presence of tertiary bases.

3. Thermal cleavage of N-diaryloxyphosphinyl-N'-arylsulfonylbenzamidines gave benzonitrile and the corresponding diaryl esters of arylsulfonylamidophosphoric acids.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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# N-DIAMINOPHOSPHINYLAROYLAMIDES

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N-Diaminophosphinylacylamides of the type  $\text{RSO}_2\text{NHPO}(\text{NHR}')_2$  have been studied quite thoroughly [1]. Several N-diaminophosphinylacylamides of the type  $(\text{ArO})_2\text{PONHPO}(\text{NHR}')_2$  have been prepared [2]. N-Diaminophosphinylacylamides of the type  $\text{RCONHPO}(\text{NHR}')_2$  have hardly been studied at all. Only N-dianilidophosphinyldichloro- and N-dianilidophosphinyltrichloroacetamides have been described and these were prepared by Steinkopf [3] by the action of aniline on the corresponding chlorides. The diacid chlorides of N-aroamidophosphoric acids of the type  $\text{ArCONHPOCl}_2$  recently became readily available [4] and this made it possible to prepare and study a series of N-diaminophosphinylaroalamides.



N-Diaminophosphinylaroalamides (Table 1) are quite high-melting, colorless, crystalline substances, which are insoluble in aqueous solutions of alkaline carbonate and acids and soluble in dilute solutions of caustic alkalis. They are precipitated unchanged from alkaline solutions by acids. N-Diaminophosphinylaroalamides are very difficult to hydrolyze and are practically unchanged by boiling for 16 hr in 2 N aqueous alcohol solutions of sodium hydroxide or hydrochloric acid.

It was found recently that the reaction of phosphorus pentachloride with diesters of aroamidophosphoric acids forms acid chlorides of N-diaroxyphosphinyliminocarboxylic acids [5].



It might have been expected that N-diaminophosphinylaroalamides would react analogously with phosphorus pentachloride:



i.e., to form acid chlorides of N-diaminophosphinyliminocarboxylic acids. However, it was found that the reaction of phosphorus pentachloride with N-diaminophosphinylaroalamides even at 50–60° proceeds almost quantitatively according to the scheme:



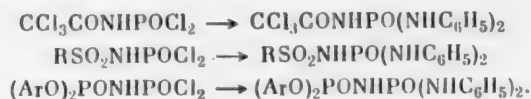
This is probably explained by the fact that the acid chlorides of N-diaminophosphinyliminocarboxylic acids formed initially decomposed at the moment of formation by a scheme analogous to the thermal cleavage of acid chlorides of N-dichlorophosphinyliminocarboxylic acids [6].



The preparation method, analytical data and chemical properties (see above) quite strictly demonstrate the structure of N-diaminophosphinyldiarylamides, including N-dianilidophosphinylbenzamide (table). Nonetheless, Titherley and Worrel [7] reported that the action of aniline on the diacid chloride of benzoylamidophosphoric acid gave an almost quantitative yield of the N-benzoylamide of N'-phenylmetaphosphimic acid, but gave no demonstration of its structure.



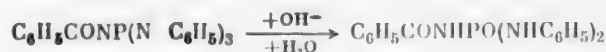
The formation of a substance with this structure is very improbable, as there are no known monomeric compounds of pentavalent phosphorus in which the phosphorus atom has a coordination number of three or, in other words, is connected by two formally double bonds to two other atoms. In addition, the N-diaminophosphinylacetyl amides listed above [1-3] were obtained by the reaction of the corresponding diacid chlorides of acylamidophosphoric acids with aromatic amines. In all cases the reactions were almost quantitative:



Thus, there is every reason to assume that the data of Titherley and Worrel are incorrect and in actual fact the reaction of the diacid chloride of benzoylamidophosphoric acid with aniline yields N-dianilidophosphinylbenzamide.



N-Dianilidophosphinylbenzamide was synthesized exactly under the conditions described by Titherley and Worrel and also in dioxane and benzene solutions. In all cases the crude product was obtained in a yield of 95-96 % calculated on the formula of N-dianilidophosphinylbenzamide, and 129-131 % calculated on the formula  $\text{C}_6\text{H}_5\text{CONHPO}(=\text{NC}_6\text{H}_5)$ . The crude product could not have contained considerable amounts of impurities, as its melting point differed from that of the pure substance by only 3-4°. Analysis data for nitrogen and phosphorus also corresponded to the formula of N-dianilidophosphinylbenzamide and not the N-benzoylamide of N'-phenylmetaphosphimic acid. N-Dianilidophosphinylbenzamide was also obtained by alkaline hydrolysis of trianilidophosphazobenzoyl.



A mixed melting point with the product obtained by the reaction of the diacid chloride of benzoylamidophosphoric acid with aniline was not depressed.

Thus, it may be regarded as strictly demonstrated that the action of aniline on N-dichlorophosphinylbenzamide yields only N-dianilidophosphinylbenzamide and the data of Titherley and Worrel [7] on the formation of the N-benzoylamide of N'-phenylmetaphosphimic acid are incorrect.

#### EXPERIMENTAL

N-Diaminophosphinyldiarylamides (table). With continuous stirring and cooling in iced water, a solution of 0.08 mole of the amine in 10 ml of dry dioxane was added to a solution of 0.02 mole of the diacid chloride of the N-arylamidophosphoric acid in 40 ml of dry dioxane or benzene and the mixture left for 1.5-2 hr. The precipitate of the amine hydrochloride was removed and the solvent evaporated in vacuum. The residue was a compact crystalline mass or a thick oil which crystallized when rubbed with a glass rod. The crystals were collected, washed several times with water and alcohol, dried and recrystallized.

Reaction of phosphorus pentachloride with N-dianilidophosphinylbenzamide. To a suspension of 0.03 mole of N-dianilidophosphinylbenzamide in 150 ml of benzene was added 0.08 mole of phosphorus pentachloride and the mixture heated at 50-60° until the evolution of hydrogen chloride ceased completely (20-25 min). The precipitated



N-Diaminophosphinylaroylamides of the Type  $\text{ArCONHPO}(\text{NRR}')_2$

Ar	R	R'	Yield, %	M.p.	External form; crystal- lization solvent
$\text{C}_6\text{H}_5$	H	$\text{C}_6\text{H}_5$	97	215—216°	Needles; alcohol
$\text{C}_6\text{H}_5$	H	$p\text{-CH}_3\text{C}_6\text{H}_4$	66	218—220	Needles; alcohol
$\text{C}_6\text{H}_5$	$\text{C}_2\text{H}_5$	$\text{C}_2\text{H}_5$	22	99—101	Square plates; alcohol + water
$p\text{-ClC}_6\text{H}_4$	H	$\text{C}_6\text{H}_5$	84	215—216	Prisms; methanol + di- oxane
$p\text{-ClC}_6\text{H}_4$	H	$p\text{-CH}_3\text{C}_6\text{H}_4$	70	215—217	Prisms; methanol
$p\text{-ClC}_6\text{H}_4$	$\text{C}_2\text{H}_5$	$\text{C}_2\text{H}_5$	42	142—144	Needles; alcohol + water
$o\text{-NO}_2\text{C}_6\text{H}_4$	H	$\text{C}_6\text{H}_5$	76	237—238	Prisms; dioxane
$o\text{-NO}_2\text{C}_6\text{H}_4$	H	$p\text{-CH}_3\text{C}_6\text{H}_4$	81	252—253	Prisms; dioxane
$o\text{-NO}_2\text{C}_6\text{H}_4$	$\text{C}_2\text{H}_5$	$\text{C}_2\text{H}_5$	36	151—152	Needles; benzene
$m\text{-NO}_2\text{C}_6\text{H}_4$	H	$\text{C}_6\text{H}_5$	59	213—214	Prisms; alcohol
$m\text{-NO}_2\text{C}_6\text{H}_4$	H	$p\text{-CH}_3\text{C}_6\text{H}_4$	93	229—230	Prisms; alcohol + di- oxane
$m\text{-NO}_2\text{C}_6\text{H}_4$	$\text{C}_2\text{H}_5$	$\text{C}_2\text{H}_5$	57	119—121	Needles; alcohol + water
$p\text{-NO}_2\text{C}_6\text{H}_4$	H	$\text{C}_6\text{H}_5$	86	225—226	Prisms; alcohol + di- oxane
$p\text{-NO}_2\text{C}_6\text{H}_4$	H	$p\text{-CH}_3\text{C}_6\text{H}_4$	85	216—219	Prisms; alcohol + di- oxane
$p\text{-NO}_2\text{C}_6\text{H}_4$	$\text{C}_2\text{H}_5$	$\text{C}_2\text{H}_5$	64	187—189	Needles; acetone
$3,5\text{-(NO}_2)_2\text{C}_6\text{H}_3$	H	$\text{C}_6\text{H}_5$	94	226—228	Needles; alcohol
$3,5\text{-(NO}_2)_2\text{C}_6\text{H}_3$	H	$p\text{-CH}_3\text{C}_6\text{H}_4$	90	238—239	Prisms; nitrobenzene
$3,5\text{-(NO}_2)_2\text{C}_6\text{H}_3$	$\text{C}_2\text{H}_5$	$\text{C}_2\text{H}_5$	45	159—161	Plates; alcohol
$p\text{-CH}_3\text{OC}_6\text{H}_4$	H	$\text{C}_6\text{H}_5$	95	208—210	Prisms; alcohol
$p\text{-CH}_3\text{OC}_6\text{H}_4$	H	$p\text{-CH}_3\text{C}_6\text{H}_4$	99	202—204	Needles; alcohol
$p\text{-CH}_3\text{C}_6\text{H}_4$	$\text{C}_2\text{H}_5$	$\text{C}_2\text{H}_5$	88	128—130	Rhombs; ligroin

- <sup>+</sup> — Readily soluble at 20°; + — readily soluble at boiling point, — — sparingly soluble at  
 •• Found %: P 8.81, 8.64. Calculated %: P 8.81.  
 ••• Found %: Cl 10.46, 10.62. Calculated %: Cl 10.25.

crystals of the dianilidochlorophosphate were collected, washed with benzene ( $2 \times 3$  ml) and ether ( $2 \times 3$  ml), and dried. The yield was 95%. Recrystallization from alcohol gave needles with m.p. 171—172°, which corresponds to literature data [8]. The mother solution was evaporated and the remaining benzonitrile distilled. The yield of benzonitrile was about 100%. The compound was identified by the boiling point and the refractive index. Phosphorus pentachloride reacted analogously with the other N-diaminophosphinylaroylamides.

N Found, %	Formula	N Calculated, %	Solubility*						
			C <sub>6</sub> H <sub>6</sub>	alcohol	acetone	ether	ligroin	chloroform	CCl <sub>4</sub>
11.94, 11.97	C <sub>19</sub> H <sub>18</sub> O <sub>2</sub> N <sub>3</sub> P**	11.95	—	—	+	—	=	—	=
10.81, 10.91	C <sub>21</sub> H <sub>22</sub> O <sub>2</sub> N <sub>3</sub> P	11.07	—	—	+	—	=	+	=
13.13, 13.14	C <sub>15</sub> H <sub>25</sub> O <sub>2</sub> N <sub>3</sub> P	13.48	+	+	+	+	+	+	+
10.50, 10.54	C <sub>19</sub> H <sub>17</sub> O <sub>2</sub> N <sub>3</sub> PCl	10.88	=	+	=	=	=	+	=
10.34, 10.36	C <sub>21</sub> H <sub>21</sub> O <sub>2</sub> N <sub>3</sub> PCl	10.14	=	+	=	=	+	=	=
11.81, 11.82	C <sub>15</sub> H <sub>25</sub> O <sub>2</sub> N <sub>3</sub> PCl***	12.14	+	—	+	—	=	+	=
14.35, 14.32	C <sub>19</sub> H <sub>17</sub> O <sub>4</sub> N <sub>4</sub> P	14.13	=	=	=	=	=	=	=
13.65, 13.54	C <sub>21</sub> H <sub>21</sub> O <sub>4</sub> N <sub>4</sub> P	13.19	=	=	=	=	=	=	=
15.64, 15.77	C <sub>15</sub> H <sub>25</sub> O <sub>4</sub> N <sub>4</sub> P	15.71	—	+	+	=	=	+	+
14.43, 14.26	C <sub>19</sub> H <sub>17</sub> O <sub>4</sub> N <sub>4</sub> P	14.13	=	+	+	=	=	=	=
13.07, 12.88	C <sub>21</sub> H <sub>21</sub> O <sub>4</sub> N <sub>4</sub> P	13.19	=	=	=	=	=	=	=
15.31, 15.48	C <sub>15</sub> H <sub>25</sub> O <sub>4</sub> N <sub>4</sub> P	15.71	+	+	+	+	+	+	+
13.86, 13.89	C <sub>19</sub> H <sub>17</sub> O <sub>4</sub> N <sub>4</sub> P	14.13	=	+	+	=	=	=	=
12.86, 12.94	C <sub>21</sub> H <sub>21</sub> O <sub>4</sub> N <sub>4</sub> P	13.19	=	+	+	=	=	+	=
15.65, 15.79	C <sub>15</sub> H <sub>25</sub> O <sub>4</sub> N <sub>4</sub> P	15.71	+	+	+	=	=	+	+
15.98, 16.10	C <sub>19</sub> H <sub>16</sub> O <sub>6</sub> N <sub>5</sub> P	15.86	=	—	+	=	=	—	=
14.55, 14.70	C <sub>21</sub> H <sub>20</sub> O <sub>6</sub> N <sub>5</sub> P	14.91	=	=	=	=	=	=	=
17.22, 17.07	C <sub>15</sub> H <sub>24</sub> O <sub>6</sub> N <sub>5</sub> P	17.44	+	+	+	=	=	+	+
10.92, 10.91	C <sub>20</sub> H <sub>20</sub> O <sub>3</sub> N <sub>3</sub> P	11.01	=	+	—	=	=	—	=
10.49, 10.42	C <sub>22</sub> H <sub>24</sub> O <sub>3</sub> N <sub>3</sub> P	10.25	=	+	+	=	=	+	=
12.06, 12.07	C <sub>17</sub> H <sub>28</sub> O <sub>3</sub> N <sub>3</sub> P	12.30	+	+	+	+	+	+	+

boiling point, = — insoluble at boiling point. None of the substances were soluble in water at the boiling point.

Preparation of N-diamidophosphinylbenzamide by Titherley and Worrel's method [7]. To a suspension of 0.021 mole of the diacid chloride of N-benzoylamidophosphoric acid in 30 ml of water was added 0.086 mole of aniline and the mixture ground in a mortar. The emulsion formed rapidly solidified and changed to a compact mass after 5–6 min and this was ground, sucked dry, washed with dilute hydrochloric acid, and dried. The yield was 95%. Recrystallization from alcohol gave needles with m.p. 215–216°. A second recrystallization did not raise the melt-

ing point. According to the data of Titherley and Worrel, the product melts at 226°, which does not correspond to the facts. Titherley and Worrel also gave an incorrect melting point (115° instead of 95–96°) for the diacid chloride of N-benzoylamidophosphoric acid. The solubility, chemical properties and form of the crystals of N-dianilidophosphinylbenzamide coincided with the data given by Titherley and Worrel for the product which they considered to be the N-benzoylamide of N'-phenylmetaphosphimic acid.

Preparation of N-dianilidophosphinylbenzamide from the diacid chloride of benzoylamidophosphoric acid and aniline in dioxane or benzene. With continuous stirring and cooling in iced water, a solution of 0.04 mole of aniline in 5 ml of dry dioxane was added to a solution of 0.01 mole of the diacid chloride of benzoylamidophosphoric acid in 25 ml of dry dioxane or benzene and the mixture left for 1.5–2 hr. The precipitate of aniline hydrochloride was removed (about 100% yield) and the solvent evaporated in vacuum. The residual compact crystalline mass was ground, washed with water (2 × 5 ml), alcohol (1 × 5 ml) and ether, and dried. The yield was 97% and the m.p. 211–213°. Recrystallization from alcohol gave needles with m.p. 215–216°; a second recrystallization did not raise the melting point. A mixed melting point with the product obtained by the previous method was not depressed.

Preparation of N-dianilidophosphinylbenzamide from trianilidophosphazobenzoyl. To a solution of 0.01 mole of trianilidophosphazobenzoyl (see below for preparation) in 10 ml of alcohol was added 30 ml of 0.3 N aqueous sodium hydroxide solution and the mixture boiled for 2–3 min. The alcohol was removed in vacuum, the residue made acid to Congo with concentrated hydrochloric acid, and the precipitated crystals collected. The yield was 91%. Recrystallization of the substance from alcohol gave needles with m.p. 215–217°; mixed melting points with the products obtained by the methods described above were not depressed.

Preparation of trianilidophosphazobenzoyl. With continuous stirring and cooling with iced water, a solution of 0.06 mole of aniline in 10 ml of benzene was added to a solution of 0.01 mole of trichlorophosphazobenzoyl in 30 ml of benzene and the mixture boiled on a water bath for 10–15 min. The precipitate of aniline hydrochloride was removed and the benzene evaporated in vacuum. The residual thick clear oil slowly crystallized during prolonged standing with 10 ml of ligroin and with prolonged rubbing with a glass rod. The crystals were collected, washed with ligroin and ether, and dried. The yield was 91% and the m.p. 112–115° (decomp.).

Found %: N 13.50, 13.52.  $C_{25}H_{23}ON_4P$ . Calculated %: N 13.12.

#### SUMMARY

1. The action of aniline, p-toluidine and diethylamine on the diacid chlorides of N-arylamidophosphoric acids formed the corresponding N-diaminophosphinylaroylamides.

2. The action of phosphorus pentachloride on N-diaminophosphinylaroylamides cleaved the latter to the corresponding nitriles and the acid chlorides of the corresponding diamidophosphoric acids.

3. The N-benzoylamide of N'-phenylmetaphosphimic acid described by Titherley and Worrel was actually N-dianilidophosphinylbenzamide.

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## SYNTHESIS OF $\beta$ -HALOPROPIONIC ACIDS

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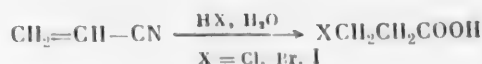
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$\beta$ -Halopropionic acids are of practical use in the synthesis of dyes, heterocyclic compounds and drugs and in particular for the preparation of  $\beta$ -alanine, pantothenic acid, propiorhodanine, etc. In addition to other preparation methods [1], the syntheses of these acids from acrylonitrile and dry hydrogen halides have been described [2]; however, these syntheses require a large expenditure of time, the use of complex apparatuses, and give yields which do not exceed 30-40% in the case of iodo derivatives.

In view of the drawbacks of the methods used, we undertook to develop a simple and convenient general method of preparing halopropionic acids from acrylonitrile. The addition of hydrogen halides to acrylonitrile is known to proceed smoothly with cooling to form a  $\beta$ -halopropionitrile or (with excess hydrogen halide) the corresponding haloimide [3].

We investigated the reaction of acrylonitrile with concentrated aqueous solutions of hydrohalic acids at the boiling point, using a bromide and sulfuric acid instead of hydrobromic acid. As our experiments showed [4, 5], under the given conditions, which hindered the polymerization of acrylonitrile, there was rapid hydrolysis of the nitrile group with simultaneous addition of the hydrogen halide;  $\beta$ -halopropionic acids were obtained in yields of 70-80%.



### EXPERIMENTAL

**$\beta$ -Chloropropionic acid.** A solution of 21.1 g of technical acrylonitrile in 140 ml hydrochloric acid (d 1.18) was boiled for 1 hr in a flask with a reflux condenser. The cooled mixture was filtered to remove ammonium chloride (10 g) and the filtrate extracted with 320 ml of ether (in 4 portions). The ether and water were distilled from the wet extract and then  $\beta$ -chloropropionic acid distilled at 105-106° (18-20 mm) and immediately solidified to a white crystalline mass with m. p. 36-37°. The yield was 30 g (68%). In an experiment with twice the amounts of reagents, we obtained 69 g (78%). After recrystallization from chloroform, the product had m. p. 41° (according to literature data [1], m.p. 39-40°).

Found %: COOH 42.1.  $\text{C}_3\text{H}_5\text{O}_2\text{Cl}$ . Calculated %: COOH 41.4.

The reaction mixture could also be distilled without extraction with ether, but the yield was then reduced to 55%. The yield was also reduced by more prolonged boiling of the reaction mixture.

Passing dry hydrogen chloride into cooled acrylonitrile with subsequent hydrolysis of the  $\beta$ -chloropropionitrile obtained yielded 62% of the acid.

**$\beta$ -Bromopropionic acid.** To 70 ml of water were added 100 ml of concentrated sulfuric acid, 90 g of potassium bromide and 16 g of redistilled acrylonitrile with cooling. The mixture obtained was boiled for 2 hr. A yellow homogeneous solution was formed after 20 min and then there was vigorous evaporation of hydrogen bromide. A deviation from the above reagent ratio led to the formation of a heavy oily layer. After 2 hr, the solution was cooled, the solidified mass filtered, and the precipitate washed with water on the filter. The combined filtrates were extracted with 400 ml of carbon tetrachloride and the precipitate with 100 ml of carbon tetrachloride.

The extracts were combined and dried with sodium sulfate and the solvent was removed as far as possible. The crystalline precipitate formed (42-44 g) was distilled at 119-120° (18 mm) [or 140-142° (45 mm)] with strong cooling of the receiver. We obtained 34-36 g (76%) of  $\beta$ -bromopropionic acid as coarse, snow-white crystals with m.p. 62-63° (literature data [1]: m.p. 62°).

Found %: COOH 29.9.  $C_3H_5O_2Br$ . Calculated %: COOH 29.4.

The use of other salts instead of potassium bromide led to a decrease in the acid yield.

$\beta$ -Iodopropionic acid. A mixture of 220 ml of technical hydriodic acid ( $d$  1.52) or a corresponding amount of acid of another concentration (but not less than 40%) and 3-4 g of red phosphorus was heated under reflux until the color disappeared. The solution was allowed to cool, 20 ml of acrylonitrile introduced through the condenser, and heating recommenced.

After being boiled for 4 hr, the reaction solution was left overnight and the iodopropionic acid (14 g) which precipitated as coarse, colorless plates collected. To the filtrate was added 2 g of phosphorus and then more than 2/3 of the total volume removed by distillation at 100-127° until there was voluminous crystallization in the flask; this made it possible to collect a considerable part of the unreacted hydriodic acid. The residue in the flask was filtered and the precipitate recrystallized from the minimal amount of water with charcoal and a small amount of hyposulfite to give a further 27-29 g of product. We obtained a total of about 42 g (70%) of  $\beta$ -iodopropionic acid as lustrous platelets with m. p. 81°, which turned pink in light.

Found %: COOH 21.7.  $C_3H_5O_2I$ . Calculated %: COOH 22.5.

#### SUMMARY

Concentrated aqueous solutions of hydrogen halides added readily to acrylonitrile at the boiling point and, after hydrolysis of the nitrile group, formed the corresponding  $\beta$ -halopropionic acids in high yields. It was possible to use concentrated aqueous solutions of potassium bromide and sulfuric acid instead of hydrobromic acid for the synthesis of  $\beta$ -bromopropionic acid.

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# PREPARATION OF ALKYPHENOLS BY REARRANGEMENT OF ALKYL ARYL ALUMINATES

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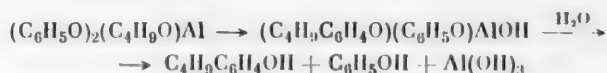
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In studying aliphatic alcoholates of aluminum, V. E. Tishchenko [1] found that they decompose at 240-320° with the formation of mainly ethers and also alkenes and products of more extensive decomposition. Aluminum phenolates are more stable [2]. At about 300°, aluminum phenolate catalyzes the alkylation of phenols by alkenes [3, 4].

In view of the above, we considered that when mixed aliphatic-aromatic alcoholates of aluminum were heated to the decomposition point (250-300°), the alkyl would enter the aromatic nucleus. This hypothesis was confirmed by experiment. The reaction proceeded best with diphenyl alkyl aluminates; subsequent hydrolysis yielded alkyl phenols.



Simultaneously with alkylation there was a side reaction, analogous to the reactions studied by Tishchenko [1]:



For identification, the alkene was absorbed with bromine water to yield the corresponding dibromoalkane. The alcohol formed could be isolated by distillation and identified by the usual methods. The alcohol reduced the reaction temperature, hampering alkylation. Excess aluminum was used to prevent this and the alcohol obtained was rapidly converted to the aluminum alcoholate. It was possible to carry out the reaction without excess aluminum with distillation of the alcohol formed; in this case the reaction temperature was slightly lower and the alkylphenol yields were correspondingly lower. We should note that ethers were not obtained under our conditions.

In the presence of catalysts such as  $\text{KAl}(\text{SO}_4)_2$ , the side reaction predominated and alkylation did not occur. Thus, it cannot be assumed that the reaction mechanism consists of alkylation of aluminum phenolates by the alkene. Alkenes alkylate phenols in the presence of aluminum phenolate only under pressure [3, 4]. It is evident that an aluminum alcoholate catalyzes alkylation in the same way as aprotic acids ( $\text{AlCl}_3$ ,  $\text{BF}_3$ , etc.). The reaction is partly similar to the alkylation of phenol by ethanol and isopropanol over alumina [5] with the formation of o-ethylphenol and o-isopropylphenol, respectively. In our work the ortho-isomer also predominated in the preparation of ethyl-, isopropyl- and sec-butylphenols.

The formation of the ortho-isomer is explained by the high reaction temperature and the absence of strong acids: previous investigators also obtained predominantly or exclusively the ortho-isomer under these conditions [3, 5]. We should note that in our work the para-isomer predominated both in the alkylation of phenol with isobutylene [3] and in the synthesis of tert-butylphenols (see table, experiments 4 and 5). Stroh, Seydel and Hahn [3] considered that this is explained by secondary rearrangement of o-tert-butylphenol into p-tert-butylphenol.

The reaction we describe cannot be regarded as monomolecular, as this is incompatible with the formation of tri-tert-butylphenol from diphenyl isobutyl aluminate (see table, experiment 5). In addition, it must be considered

## Preparation of Alkylphenols by Rearrangement of Aryl Alkyl Aluminates

Exp. No.	Alkylation conditions		Alkyl (in alkylphenol)	Yield of alkylphenols			
	time, hr	temperature		g	mole	% on phenol	
						taken	reacting
1	5	260—293°	o-Ethyl	18.8	0.154	30.9	54.3
			p-Ethyl	6.1	0.05	10.0	17.7
2	5	240—270	o-Isopropyl	26.9	0.20	40.4	83
			o-sec-Butyl	20.2	0.133	27.0	65.5
3	4	260—300	p-sec-Butyl	9.6	0.04	8.5	20.7
			Dibutyl	4.13	0.02	4.1	10.1
4	3.5	250—300	o-tert-Butyl	6.1	0.0406	8.9	31
			p-tert-Butyl	12.9	0.086	17.2	66
			o-tert-Butyl	7.4	0.025	5	16.4
			p-tert-Butyl	3.8	0.049	9.8	35.0
5	12	260—300	2, 4, 6-Tri-tert-butyl	4.8	0.018	3.6	12.8
6	4	250—300	o-tert-Butyl	16	10.6	23.02	86.5
7	2.5	215—235	o-tert-Butyl	7	0.0473	9.5	89

that there is no conjugation between the alkyl and the phenyl in alkyl aryl aluminates. However, in an attempt to alkylate aluminum phenolate by aluminum butylate (see table, experiment 7), the yields were low, possibly because the decomposition temperature was low and the aluminum phenolate was insufficiently reactive with the result that the formation of isobutylene by pyrolysis of aluminum isobutylate dominated. As a rule, the percentage conversion of phenol was low. During the alkylation (rearrangement) there occurred the isomerization of alkyls (propyl to isopropyl, etc.) which is normal for ionic alkylation. The phenols obtained did not contain nonphenolic products.

## EXPERIMENTAL

The mixed aluminum alcoholates were obtained by dissolving aluminum turnings in a mixture of phenol and the alcohol in a round-bottomed flask with a long (8-bulb) reflux condenser with a calcium chloride tube. To accelerate the reaction, it was possible to heat the aluminum and phenol together until the reaction began and then add the alcohol. It was not necessary to activate the aluminum. The alcoholate was used without purification.

**Synthesis of tert-butylphenols.** The alcoholate was prepared from 13.5 g of aluminum, 94 g of phenol and 37 g of isobutanol. Then 5.4 g of aluminum was added and the mixture heated on a sand bath for 3.5 hr at 250–260° and finally at 300°. The reaction was stopped when the evolution of gases ceased (the mass stopped effervescing). The emergent gases were absorbed in bromine water in two Tishchenko bottles. The mixture was cooled, 200–250 ml of 7% sodium chloride solution added, and the mixture boiled for 2 hr (hydrolysis). The mass was then extracted several times with benzene, the extracts dried with baked magnesium sulfate, the benzene removed, and the residue distilled at 50 mm. Unchanged phenol (80.8 g) distilled up to 104–106°; the fraction boiling at 130–155° (21 g) was redistilled on a column with a glass packing (40 cm in height, 12 theoretical plates) at 50 mm. This yielded 1 g of unchanged phenol at 104–106° and 6.1 g of o-tert-butylphenol at 136–137°:

$d_4^{20}$  1.0856,  $n_D^{20}$  1.5214 (which corresponds to literature data [6]),  $M_R$  46.38; calc. 46.42.

At 150–152° there distilled 12.9 g of p-tert-butylphenol with m. p. 97.5°; according to literature data: m. p. 97–99° [6]. The yields on the phenol taken were 8.12 and 17.2% (total 25.32%) for the ortho- and para-isomers, respectively; the yields on the phenol reacting were 31 and 66% (total 97%), respectively. By the usual method [7], the two isomers were converted into tert-butyl-phenoxyacetic acids with m.p. 147.5–148 and 86°, respectively; according to literature data, 148 and 86° [6,8].



Unchanged phenol g	B. p. (pressure in mm)	M. p. of phenoxy- acetic acid	Other characteristics of product	Literature
67.3	123—125°(50)	138—140°	—	[4]
	136—137 (50)	97	—	[10]
71	132—135	128—130	—	[3, 9]
	62 (5)	114	$d_0^{20}$ 1.002, $n_D^{20}$ 1.5210, MR 46.62; calculated 46.42	[11, 12]
74.7	86 (5)		M. p. 57°	[12]
	112 (3)		Soluble in alcoholic alkali of Claisen [3] and Cohen [10]	
81.8	136—137 (50)	147.5—148	$d_0^{20}$ 0.9856, $n_D^{20}$ 1.5214	[6]
	150—152 (50)	86	M. p. 98-99°	[8, 9]
80.93	See exp. 4		—	
	See exp. 4			
	175—178 (50)		M. p. 131°. Insoluble in alco- holic alkali of Claisen and Cohen Found %: C 82.51; H 11.35. $C_{12}H_{10}O$ . Calculated %: C 82.44 H 11.45	[3, 10, 11]
72.4	See exp. 4			
84	See exp. 4			

The heavy oily product from the Tishchenko bottles was collected, washed with potassium carbonate solution, dried, and distilled twice on a column 15 cm high. We obtained 43.2 g of dibromoisobutane with b. p. 149-152° and  $d_0^{20}$  1.5111. Literature data: b. p. 149-152° and  $d_0^{20}$  1.51186 [9].

If the heating time was increased to 12 hr and the amount of aluminum added to the prepared aluminate increased to 10.8 g, then 2, 4, 6-tri-tert-butylphenol was obtained in addition to o- and p-tert-butylphenols (see table, experiment 5).

The experiments with ethyl, propyl and butyl diphenyl aluminates were analogous and yielded ethyl-, isopropyl- and sec-butylphenols, respectively. All the constants of the products corresponded to literature data. The corresponding dibromoalkanes were obtained in the absorber bottles with bromine water. The experimental results are given in the table. In experiments 1-5 we used 1 mole of phenol and 0.5 mole of the corresponding alcohol. In experiment 6 we used 0.5 mole of phenol and 1 mole of isobutanol. In experiment 7, aluminum phenolate was alkylated with isobutyl aluminate. A mixture of 102 g of aluminum phenolate, 42 g of aluminum isobutylate and 5.4 g of aluminum turnings was boiled on a sand bath. The temperature rose from 215 to 235° over 2.5 hr, then the evolution of gases ceased, over 0.5 hr the temperature rose to 260°, and the mixture began to decompose. The mixture was treated as above.

#### SUMMARY

It was shown that the alkyl migrates to the benzene ring when alkyl aryl aluminates are heated. Hydrolysis of the reaction products yielded alkylphenols. Hypotheses are put forward on the reaction mechanism.

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## THIOSULFONIC ACIDS

### VI. SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF TRICHLOROMETHYL AND METHYL ESTERS OF SOME THIOSULFONIC ACIDS

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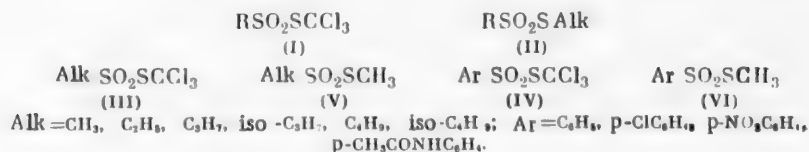
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Trichloromethyl esters of thiosulfonic acids (I) were described recently by American investigators [1] as highly active fungicides; according to these authors, the nature of the radical R has little effect on the fungicidal properties of these compounds. Nonetheless, many years work by one of us in cooperation with microbiologists has shown [2,3] that the antimicrobial properties of thiosulfonic esters (II) depend to a considerable extent on the nature of precisely this radical of the thiosulfonic acid and this caused us to doubt the conclusions of the investigators mentioned. In the present work we undertook the synthesis of the trichloromethyl esters (III) and (IV) of some alkane- and arene-thiosulfonic acids in order to check the report of these authors and to find preparations of practical interest.

At the same time, we decided that it was interesting to prepare the corresponding methyl esters (V) and (VI) in order to study the antimicrobial properties of these compounds and thus determine the effect of the chlorine atoms on the fungicidal activity of thiosulfonic esters; the latter seemed worthy of attention, as according to data of previous work [2, 3], the esters (II) which do not contain chlorine atoms generally have fungicidal activity.



The trichloromethyl esters of alkane- and arene-thiosulfonic acids were synthesized by a known procedure [4] by the reaction of sodium sulfinates with perchloromethyl mercaptan:



The alkanesulfinates were obtained by reduction of the corresponding sulfonyl chlorides with zinc dust in alcohol with subsequent conversion of the zinc salts into sodium salts with sodium carbonate [5]; the arenesulfinates were prepared by reduction of sulfonyl chlorides with sodium sulfite [10].

The trichloromethyl esters of alkanethiosulfonic acids were synthesized in anhydrous carbon tetrachloride with heating on a water bath for 3-4 hr and subsequent filtration of the reaction mixture, removal of the solvent in vacuo, and purification of the residue obtained; in the case of arene-thiosulfonic esters, the analogous reaction proceeded readily in an aqueous medium, but required special purification of the starting salts. Under these conditions, the trichloromethyl esters began to precipitate almost immediately and the reaction was complete in half an hour.

The methyl esters of thiosulfonic acids were prepared as we described previously [6] by the reaction of potassium thiosulfonates with methyl iodide at room temperature.

The thiosulfonic esters synthesized, most of which were prepared for the first time, are given in the table.

The trichloromethyl esters of alkanethiosulfonic acids were colorless, oily liquids, with the exception of the esters of methane- and 2-propanethiosulfonic acids, which were crystalline substances; they all had an unpleasant choking odor, reminiscent of the odor of perchloromethyl mercaptan, distilled in vacuum (1-2 mm), dissolved sparingly in water, and dissolved readily in alcohol, ether and other organic solvents. The methyl esters of the same thiosulfonic acids had physical properties similar to those of the trichloromethyl esters: they were all colorless liquids with the specific odor of garlic, distilled in vacuum at a pressure of 1-2 mm, and were similar in solubility to the trichloromethyl esters, with the exception of methyl methanethiosulfonate, which was readily soluble in water. There was a similar analogy between the properties of trichloromethyl and methyl esters of arenethiosulfonic acids; we should note only that these substances had hardly any unpleasant odor.

The molecular refractions of the trichloromethyl and methyl esters calculated from the atomic refractions differed from the experimental values by considerable amounts which exceeded the possible experimental errors, but for each series of esters, these differences were of the same order; only benzenethiosulfonic esters gave deviations which differed from those of the other esters of the same series. However, if we consider the additional correction (exaltation) which we proposed previously [7] for alkyl esters of benzenethiosulfonic acid and took as equal to + 0.4, then  $\Delta MR$  for methyl benzenethiosulfonate will equal - 0.421 and that for the trichloromethyl ester will equal + 0.937, i. e., will lie within the same range as  $\Delta MR$  for the other methyl and trichloromethyl esters of thiosulfonic acids. The latter not only confirms the accuracy of the proposed exaltation on conjugation of the benzene nucleus with the thioester group, which equals + 0.4, but also shows that the introduction of a trichloromethyl group into thiosulfonic esters makes it necessary to consider an additional correction (exaltation), equal to + 0.9 on the average, in calculating the molecular refractions of these compounds; this correction equals - 0.35 for methyl esters. The differences between the experimental molecular refractions and the calculated values will then lie within the limits of experimental error.

It should be noted that the opposite signs of the exaltations for the trichloromethyl and methyl groups correspond to their different electronic effects on the conjugation system in the molecules of thiosulfonic esters.

A study of the antimicrobial activity of thiosulfonic esters which was made in the Institute of Microbiology, Academy of Sciences Ukr. SSR, showed\* that the trichloromethyl esters are less active than the methyl esters toward gram-positive, gram-negative and acid-fast bacteria, but are much more active toward pathogenic fungi. The trichloromethyl esters of alkanethiosulfonic acids were only slightly superior to the analogous esters of arenethiosulfonic acids, which would seem to confirm the opinion of the American investigators.

However, a different picture was revealed by the study of the action of the same esters on phytopathogenic fungi which was carried out by the Scientific Institute of Fertilizers and Insectofungicides [9].

The trichloromethyl esters of alkanethiosulfonic acids were also found to be the most active of all the esters tested toward the fungi *Diplodia zeae*, *Alternaria radicina*, *Verticillium dahliae*, *Fusarium vasinfectum* and *Fusarium oxysporum* under laboratory conditions, but they were much superior to the analogous esters of arenethiosulfonic acids, which refutes the opinion of the American investigators that trichloromethyl esters of different thiosulfonic acids, regardless of the nature of the latter, are equivalent in fungicidal action. The methyl esters of alkanethiosulfonic acids showed such a high fungicidal activity under the same conditions that they were not only far superior to the trichloromethyl esters of arenethiosulfonic acids, but even approached the activity of the trichloromethyl esters of alkanethiosulfonic acids. Thus, replacement of the hydrogen atoms in the methyl group of the methyl esters of thiosulfonic acids by chlorine atoms increased the activity of these compounds to only a very small extent. It should be noted in particular that both the trichloroethyl and methyl esters of alkanethiosulfonic acids showed a considerably higher activity than the well-known fungicides figone, captan, and zineb at the same concentrations.

#### EXPERIMENTAL\*\*

Sodium methane sulfinate. A 57.2 g sample of methanesulfonyl chloride was dissolved in five times the amount of anhydrous alcohol; 32.5 g of zinc dust was added in small portions to the solution with stirring and cooling so that the temperature of the reaction mixture remained at 25-30°. The reaction mixture was then heated to 50°, kept at this temperature for 1 hr, heated to boiling, and filtered to remove traces of zinc and impurities. The zinc methanesulfinate which precipitated from the filtrate was collected, washed with cold anhydrous alcohol and

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\*\* With the help of L. M. Khovalko.

Trichloromethyl and Methyl Esters of Thiosulfonic Acids  $\text{RSO}_2\text{SR}'$ 

No.	R	R'	Formula	M. p.	B. p. (pressure in mm)	Sulfur content, %		$n_D^{20}$	$M_R$		Yield, %
						found	calc.		found	calc.	
1	$\text{CH}_3$	( $\text{Cl}_3$ )	$\text{C}_2\text{H}_3\text{O}_3\text{S}_2\text{Cl}_3$	56 <sup>a</sup>	103 <sup>a</sup> (2)	27.94	28.21	—	—	—	38.3
2	$\text{C}_2\text{H}_5$		$\text{C}_3\text{H}_5\text{O}_3\text{S}_2\text{Cl}_3$	—	108—109 (2)	26.33	26.46	—	—	—	29.5
3	$\text{C}_3\text{H}_7$		$\text{C}_4\text{H}_7\text{O}_3\text{S}_2\text{Cl}_3$	—	120—121 (2)	24.90	24.82	—	—	—	30.9
4	iso- $\text{C}_3\text{H}_7$		$\text{C}_4\text{H}_7\text{O}_3\text{S}_2\text{Cl}_3$	38	107—108 (1)	24.90	25.05	—	—	—	17.5
5	$\text{C}_4\text{H}_9$		$\text{C}_5\text{H}_9\text{O}_3\text{S}_2\text{Cl}_3$	—	117—118 (0.5)	23.61	23.75	—	—	—	28.9
6	iso- $\text{C}_4\text{H}_9$		$\text{C}_5\text{H}_9\text{O}_3\text{S}_2\text{Cl}_3$	—	109 (1)	23.61	23.80	—	—	—	68.7
7	$\text{C}_6\text{H}_{13}$		$\text{C}_7\text{H}_{13}\text{O}_3\text{S}_2\text{Cl}_3$	—	77 (10 <sup>-2</sup> )	21.99	22.19	—	—	—	71.2
8	p- $\text{ClC}_6\text{H}_4$ *		$\text{C}_7\text{H}_9\text{O}_3\text{S}_2\text{Cl}_3$	59—60	—	19.67	19.64	—	—	—	67.0
9	p- $\text{NO}_2\text{C}_6\text{H}_4$ *		$\text{C}_7\text{H}_9\text{O}_3\text{S}_2\text{Cl}_3$	89—90	—	19.05	19.01	—	—	—	49.3
10	p- $\text{CH}_3\text{CONHC}_6\text{H}_4$ *		$\text{C}_9\text{H}_{11}\text{O}_3\text{NS}_2\text{Cl}_3$	158—159	—	18.39	18.28	—	—	—	68.0
11	$\text{CH}_3$ *	( $\text{Cl}_3$ )	$\text{C}_3\text{H}_6\text{O}_2\text{S}_2$	—	67—68 (0.3)	50.82	50.81	—	—	—	40.4
12	$\text{C}_2\text{H}_5$ *		$\text{C}_3\text{H}_8\text{O}_2\text{S}_2$	—	88—89 (1)	45.73	45.70	—	—	—	42.2
13	$\text{C}_3\text{H}_7$ *		$\text{C}_4\text{H}_{10}\text{O}_2\text{S}_2$	—	100—101 (1)	41.58	41.72	—	—	—	46.0
14	iso- $\text{C}_3\text{H}_7$	( $\text{Cl}_3$ )	$\text{C}_4\text{H}_{10}\text{O}_2\text{S}_2$	—	86—87 (1)	41.58	41.50	—	—	—	52.7
15	$\text{C}_4\text{H}_9$		$\text{C}_5\text{H}_{12}\text{O}_2\text{S}_2$	—	79—80 (0.1)	38.11	38.21	—	—	—	36.6
16	iso- $\text{C}_4\text{H}_9$		$\text{C}_5\text{H}_{12}\text{O}_2\text{S}_2$	—	89—90 (1)	38.11	38.31	—	—	—	62.4
17	$\text{C}_6\text{H}_{13}$		$\text{C}_7\text{H}_{16}\text{O}_2\text{S}_2$	—	131—132 (1)	34.06	34.22	—	—	—	54.0
18	p- $\text{ClC}_6\text{H}_4$	( $\text{CH}_3$ )	$\text{C}_7\text{H}_9\text{O}_2\text{S}_2\text{Cl}$	33—34	95—96 (10 <sup>-4</sup> )	28.79	28.63	—	—	—	61.8
19	p- $\text{NO}_2\text{C}_6\text{H}_4$		$\text{C}_7\text{H}_9\text{O}_2\text{NS}_2$	95—96	—	27.49	27.42	—	—	—	47.7
20	p- $\text{CH}_3\text{CONHC}_6\text{H}_4$		$\text{C}_9\text{H}_{11}\text{O}_2\text{NS}_2$	62—63	—	26.14	25.91	—	—	—	44.0

\* Esters described in the literature [1, 8]: the constants of products No. 5 and 7 have not been given previously, while esters No. 11 and 12 were prepared by the American investigators [8] by the action of elementary chlorine on solutions of the corresponding disulfides or mixtures of the disulfides in glacial acetic acid. The esters No. 11 and 12 which we obtained had the same boiling points as the methyl esters of methane- and ethanethiosulfonic acids described in [8].

\*\* As in previous work [6, 7], the refractions of the  $\text{SO}_2$  group and the sulfide sulfur were taken as equal to 8.63 and 8.00 respectively; the exaltation of the group- $\text{SO}_2\text{S}$  was taken as equal to +0.6. For the benzenethiosulfonic esters (Nos. 7 and 17) we assumed additional exaltation on conjugation with the nucleus, equal to +0.4.

\*\*\* The yields are given for the pure products (after 3-4 vacuum distillations for the liquid esters).

dried in vacuum. The yield of the zinc salt was 43.5 g (78.3%). The salt was heated and stirred with an aqueous solution of sodium carbonate (20.4 g in 80 ml of water). The reaction mixture was boiled for 1 hr and filtered free from the precipitate of zinc salts and the filtrate evaporated to dryness. The yield of sodium methanesulfinate was 26 g (73.3%). The dry sodium sulfinate was used for the synthesis of the trichloromethyl ester without further purification.

The trichloromethyl esters of alkane- and arenethiosulfonic acids were obtained by the reaction of sodium sulfinate with perchloromethyl mercaptan in anhydrous benzene or an aqueous medium (for arenethiosulfonic esters). The perchloromethyl mercaptan was prepared by chlorination of carbon disulfide by the procedure in [11]. The syntheses of two esters are described as examples.

Trichloromethyl methanethiosulfonate. A 10.2 g sample of dry sodium methanesulfinate was ground in a mortar under a layer of anhydrous benzene; the suspension obtained was transferred to a flask, 18.6 g of perchloromethyl mercaptan added, the reaction mixture stirred and heated on a water bath for 5 hr and filtered, the benzene removed by distillation on a water bath, and the residue vacuum distilled. Redistillation yielded 9.5 g of a colorless product with b. p. 103° (2 mm) which crystallized readily on cooling. As the ester had a sharp choking odor reminiscent of the odor of perchloromethyl mercaptan, it was recrystallized twice from alcohol although its melting point did not change during this. The yield of the product with m. p. 56° was 88 g (38.3%).

Found %: S 28.21.  $C_2H_3O_2S_2Cl_3$ . Calculated %: S 27.94.

Trichloromethyl p-chlorobenzenethiosulfonate. Into a flask was placed 6.6 g of perchloromethyl mercaptan, and a solution of 6.4 g of sodium p-chlorobenzenesulfinate in 35 ml of water and a small amount of sodium bicarbonate were added. The reaction mixture was shaken for several minutes and the ester which precipitated from the solution was collected, washed with a large amount of cold water, and dried in air. The yield was 7.0 g (67%); the m. p. was 59-60°, which corresponds to literature data [1].

Found %: S 19.64.  $C_7H_4O_2S_2Cl_4$ . Calculated %: S 19.67.

The methyl esters of thiosulfonic acids were obtained analogously to the alkyl esters of thiosulfonic acids we described previously [6].

#### SUMMARY

1. We synthesized 20 methyl and trichloromethyl esters of alkane- and arenethiosulfonic acids, including 13 esters that have not been described in the literature.
2. The antimicrobial activity of the esters obtained is described; trichloromethyl and methyl esters of alkane-thiosulfonic acids have a high fungicidal activity which exceeds that of trichloromethyl esters of arenethiosulfonic acids and also figone, captan and zineb at the same concentrations (in laboratory experiments).

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# REACTION OF DICHLOROPYRUVIC ACID WITH PRIMARY AROMATIC AMINES

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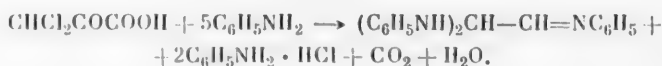
pp. 2406-2410, July, 1961

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In halogen derivatives of pyruvic acids, the halogen and the carbonyl and carboxyl groups have a high reactivity [1-3].

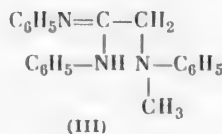
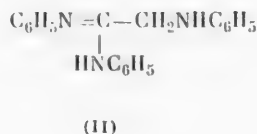
In the present work we investigated the reaction of dichloropyruvic acid (I) with some aromatic amines in the hope of preparing heterocyclic compounds.

Dichloropyruvic acid reacted with aniline at room temperature to give a salt which decomposed even during brief storage. When the mixture was heated to 80-90°, a vigorous reaction began with the evolution of carbon dioxide, water, and hydrogen chloride. The reaction product was a white crystalline substance with the composition  $C_{20}H_{19}N_3$ . Judging by the elementary composition of the product, three aniline molecules reacted with one acid molecule. One might have expected the formation of the Schiff's base of dianilinoacetaldehyde according to the scheme:



However, in actual fact the compound obtained was found to be identical with N-phenylglycine-(N',N''-diphenylamidine) (II), which was known previously.

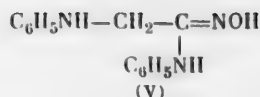
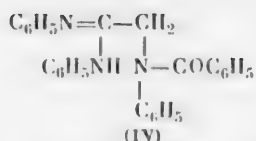
The structure of the compound (II) was demonstrated by a series of reactions. The compound formed a hydrochloride with the composition  $C_{20}H_{19}N_3 \cdot 2HCl$ ; consequently, three nitrogen atoms are present in the functional groups, of which only two are capable of adding HCl. The compound obtained did not give a diazo compound with an acidified solution of  $NaNO_2$ , as would have been the case had there been a primary amino group present, but formed a very unstable N-nitroso compound with m. p. 102-103°. This substance could not be isolated in a pure form as a result of its instability; however, the presence of a nitroso group was clearly demonstrated by an indophenol reaction [5]. The substance (II) underwent other reactions characteristic of a secondary amino group. For example, it was methylated readily by dimethyl sulfate; one hydrogen atom was replaced by a methyl group to form a compound with the composition  $C_{21}H_{21}N_3$ , to which we assigned the structure of N-phenyl-N-methylglycine-(N',N''-diphenylamidine) (III).



This compound gave a hydrochloride with two molecules of hydrogen chloride. Benzoylation of the compound studied with benzoyl chloride yielded a derivative with the composition  $C_{27}H_{23}N_3O$  (IV). It was found to be identical with N-phenyl-N-benzoylglycine-(N',N''-diphenylamidine), which was obtained by the method described in [6].

When the substance (II) obtained from dichloropyruvic acid was treated with hydroxylamine, the phenylimido group was replaced by an oxime group. From the reaction products we isolated aniline and previously unknown N-phenylglycine-N-phenylamidoxime (V).

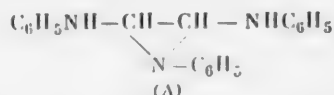




The structure of the compound (V) was confirmed by hydrolysis in the presence of mineral acid to yield the anilide of anilinoacetic acid, which has been described in the literature.

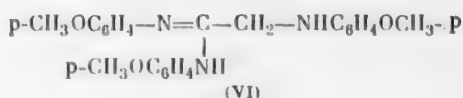
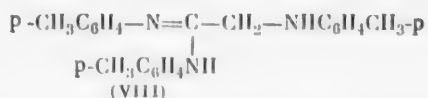
The compound described under the name of "N-phenylglycine-(N',N"-di-phenylamidine)" has also been assigned the structure of N-phenyl- $\alpha,\alpha'$ -dianilinoethylenimine by some investigators [7].

On the basis of the method of preparing the compound from dichlorophyruvic acid and aniline it would seem to be more logical to represent its structure in the form of N-phenyl- $\alpha,\alpha'$ -dianilinoethylenimine (A).



However, the compound we obtained did not undergo reactions characteristic of the ethylenimine ring.

The reaction of dichloropyruvic acid with excess p-toluidine and p-anisidine yielded N-p-tolylglycine-(N',N"-di-p-tolylamidine) (VIII) and N-p-methoxyphenylglycine-(N',N"-di-p-methoxyphenylamidine) (VI).



The yields were 90 and 54 %, respectively (calculated on the dichloropyruvic acid). These compounds had indefinite melting points and therefore they were identified in the form of the benzoyl derivatives (IX) and (VII). The benzoyl derivatives of the compounds obtained were found to be identical with the benzoyl derivatives of N-p-tolylglycine-(N',N"-di-p-tolylamidine) and N-p-methoxyphenylglycine-(N',N"-di-p-methoxyphenylamidine) described previously [8].

It should be noted that aromatic amines with the same substituents in the ortho-position (o-toluidine and o-anisidine) produced decarboxylation of dichloropyruvic acid, but the products formed were tarry and did not crystallize.

The authors would like to thank G. A. Razuvaev for discussing the results and valuable advice.

#### EXPERIMENTAL

Dichloropyruvic acid (I) (with 1 molecule of water of crystallization) with m. p. 119° [3] (from dichloroethane) was obtained by chlorination of propylene glycol [4].

N-Phenyl-glycine-(N',N"-diphenylamidine) (II). A mixture of 20 g of (I) and 140 g of aniline solidified when kept at room temperature for 20-30 min as a result of formation of the aniline salt with m. p. 92-93° (from a mixture of benzene and alcohol).

Found %: N 4.86, 4.90.  $\text{C}_9\text{H}_{11}\text{O}_4\text{NCl}_2$ . Calculated %: N 5.22.

When the mixture was heated on a water bath at 80-95°, immediately after the formation of the salt, vigorous evolution of  $\text{CO}_2$  began. The reaction proceeded with the evolution of heat and was complete after 15-20 min. The mixture was poured into water and substance (II) precipitated. The yield of (II) was 19 g (55% calculated on the acid); the m.p. was 168-180° (with decomp.) (from benzene). Literature data: m.p. 170° [9] and 189-190° [6].

Found %: C 80.20, 80.16; H 6.52, 6.35; N 13.80, 13.92.  $\underline{M}$  1235 (ebullioscopically in benzene).  $\text{C}_{20}\text{H}_{19}\text{N}_3$ . Calculated %: C 79.73; H 6.33; N 13.95.  $\underline{M}$  301.



The fourfold molecular weight was the result of association of the substance in solution.

Hydrochloride of (II). It had m. p. 173-177° (with decomp.). Literature data : m. p. 170° [10].

Found %: Cl 18.85, 18.90 (argentometrically).  $C_{20}H_{19}N_3 \cdot 2HCl$ . Calculated %: Cl 18.98.

N-Phenyl-N-methylglycine-(N',N''-diphenylamidine) (III). A mixture of 3.6 g of (II), 7 ml of dimethyl sulfate and 2.6 g of anhydrous  $Na_2CO_3$  was heated under reflux on a water bath for 4-5 hr. The excess dimethyl sulfate was decomposed with concentrated ammonia solution; 2.9 g of (III) precipitated as a thick mass, which solidified after several days and crystallized readily from ethanol as colorless leaflets; it had m. p. 95°.

Found %: Cl 80.14, 79.99; H 6.60, 6.29; N 13.21, 13.05.  $M$  323 (cryoscopically).  $C_{21}H_{21}N_3$ .

Calculated %: C 80.00; H 6.66; N 13.33.  $M$  315.

Hydrochloride of (III). It had m. p. 155-157°.

Found %: Cl 18.25, 18.10 (argentometrically)  $C_{21}H_{21}N_3 \cdot 2HCl$ . Calculated %: Cl 18.29.

N-Phenyl-N-benzoylglycine-(N',N''-diphenylamidine) (IV). A mixture of 4 g of (II) and 7 g of benzoyl chloride in 40 ml of benzene was heated under reflux on a water bath for 3-4 hr and the mixture left overnight; 5.7 g of the hydrochloride of (IV) precipitated. The precipitate was collected, washed several times with benzene, and then dissolved in ethanol and (IV) precipitated with concentrated ammonia solution. The yield was 3.5 g and the m. p. 143-144° (from ethanol). Literature data [6]: m. p. 142°.

Found %: C 80.28; H 5.65, 5.75; N 10.55, 10.50.  $M$  421 (cryoscopically). Equiv. 426.  $C_{27}H_{23}ON_3$ .

Calculated %: C 80.00; H 5.67; N 10.37.  $M$  405. Equiv. 405.

A mixed melting point with a preparation synthesized in accordance with literature data [6] was not depressed.

N-Phenylglycine-N'-phenylamidoxime (V). A mixture of 6 g of (II), 1.4 g of  $NH_2OH \cdot HCl$ , 1.1 g of  $Na_2CO_3$  and 8 ml of  $H_2O$  in 150 ml of methanol was heated under reflux on a water bath for 10-12 hr until the starting materials dissolved completely and then (V) was precipitated with excess water. The yield was 4.4 g and the m. p. 115-116.5° (from alcohol).

Found %: C 69.84, 69.91; H 6.29, 6.30; N 17.15, 17.20.  $C_{14}H_{15}ON_3$ . Calculated %: C 69.70; H 6.22; N 17.42.

The purified (V) was dissolved in dry benzene and dry HCl passed into the solution. This precipitated the hydrochloride of (V) with m. p. 128-130°.

Found %: Cl 22.20, 22.40 (argentometrically).  $C_{14}H_{15}ON_2 \cdot 2HCl$ . Calculated %: Cl 22.61.

The methanol was evaporated from the filtrate after separation of (V) and the aqueous portion extracted with benzene to yield 0.6 g of aniline; the latter was identified as benzanilide with m. p. 163° (m. p. 163° [11]). A mixed melting point with an authentic preparation was not depressed.

A mixture of 4 g of (V) and 20 ml of 3% hydrochloric acid was heated under reflux on a water bath for 5-6 hr. The mixture was neutralized with dilute ammonia solution. On standing, the mixture deposited 1.3 g of anilinoacetanilide with m. p. 112-113° (from a mixture of ethanol and water). Literature data [12]: m. p. 113°. A mixed melting point with anilinoacetanilide obtained by the method described in [12] was not depressed.

N-p-Methoxyphenylglycine-(N', N''-di-p-methoxyphenylamidine) (VI). A mixture of 10 g of (I) and 50 g of p-anisidine was heated in a beaker on a water bath to 80-90°. When the evolution of  $CO_2$  had ceased, the reaction mixture was poured into water and then washed several times with 85% aqueous ethanol for the removal of p-anisidine and its hydrochloride. The yield of (VI) was 12 g [54% calculated on (I)]; the m. p. was 166-167.5° (from benzene). Literature data [8]: m. p. 158-159°.

Found %: N 10.42.  $C_{23}H_{25}O_3N_3$ . Calculated %: N 10.74.

N-p-Methoxyphenyl-N-benzoylglycine-(N',N''-di-p-methoxyphenylamidine) (VII). From 1.5 g of (VI) and 3 g of benzoyl chloride in 20 ml of benzene, by the same method as in the preparation of (IV), we obtained 1 g of (VII) with m. p. 127-128°.

Found %: C 73.08, 72.90; H 6.04, 6.00; N 8.40, 8.20.  $C_{30}H_{29}O_4N_3$ . Calculated %: C 72.72; H 5.85; N 8.48.

A mixed melting point with the analogously obtained derivative of N-p-methoxyphenylglycine-(N',N"-di-p-methoxyphenylamidine) synthesized by a known method [8] was not depressed.

N-p-Tolylglycine-(N',N"-di-p-tolylamidine) (VIII). From 10 g of (I) and 50 g of p-toluidine by a method analogous to the preparation of (VI), we isolated 18 g of (VIII). The yield was 90% [calculated on (I)]; the m. p. was 157-163° (from benzene). Literature data [8]; m. p. 157°.

Found %: C 79.99, 79.65; H 7.08, 6.85; N 11.88, 11.86.  $C_{23}H_{25}N_3$ . Calculated %: C 80.46; H 7.28; N 12.33.

N-p-Tolyl-N-benzoylglycine-(N',N"-di-p-tolylamidine) (IX). From 2.3 g of (VIII) and 3 g of benzoyl chloride in 20 ml of benzene by a method analogous to the synthesis of (IV), we obtained 2.8 g of (IX) with m. p. 176-177.5°.

Found %: C 80.44, 80.34; H 6.48, 6.39; N 9.20, 9.02. Equiv. 458.  $C_{30}H_{29}ON_3$ . Calculated %: C 80.53; H 6.48; N 9.39. Equiv. 447.

A mixed melting point with the analogously obtained derivative of N-p-tolylglycine-(N',N"-di-p-tolylamidine) synthesized by a known method [8] was not depressed.

#### SUMMARY

The reaction of dichloropyruvic acid with aniline, p-anisidine and p-toluidine yielded N-phenylglycine-(N',N"-diphenylamidine), N-p-methoxyphenylglycine-(N',N"-di-p-methoxyphenylamidine) and N-p-tolylglycine-(N',N"-di-p-tolylamidine), respectively.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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# DETECTION OF A THREE-MEMBERED RING IN TERPENE COMPOUNDS BY INFRARED SPECTRA

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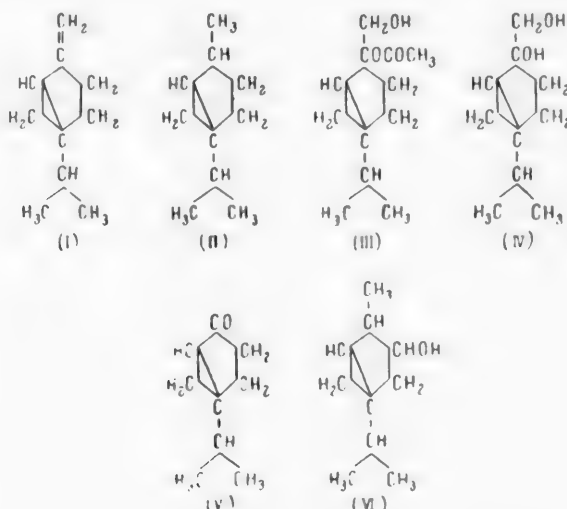
Original article submitted July 6, 1960

The detection of a cyclopropane ring in the molecule of an organic compound is always of definite interest. The presence of a three-membered ring is usually determined from the molecular refraction, which, in accordance with investigations of L. A. Chugaev et al. [1], is characterized by an exaltation of 0.7 in the case of compounds of the cyclopropane series. For crystalline compounds and compounds with a high molecular weight, the accuracy of the molecular refraction determination is considerably reduced.

The communication of Cole [2] on the possibility of detecting a cyclopropane ring by infrared absorption spectra is therefore of great interest. According to Cole, for such compounds as  $\alpha$ -thujene, thujane and 3, 5-cyclocholestan, in the region of C-H valence vibrations there are absorption bands at 3042, 3058 and 3050  $\text{cm}^{-1}$ , respectively, which correspond to the  $\text{CH}_2$  group in the cyclopropane ring. This band is absent from the spectrum of camphane, which has a three-membered ring that does not contain a  $\text{CH}_2$  group.

On the other hand, the literature also contains papers in which it is concluded that a three-membered ring cannot be detected by infrared spectra. Thus, Allen et al. [3] compared the infrared spectra of 18 compounds whose molecules contain a three-membered ring and found corresponding bands in the region of 3096-3012  $\text{cm}^{-1}$  for only the three simplest compounds with unsubstituted  $\text{CH}_2$  groups in the ring. The spectra of compounds with several substituents of an aromatic nature normally did not show the corresponding bands (sometimes even when unsubstituted  $\text{CH}_2$  groups were present in the ring).

It was therefore extremely desirable to check the accuracy of Cole's observations on a series of other substances. We had available the following bicyclic terpenes containing a three-membered ring: sabinene (I), sabinane (II), sabinene glycol monoacetate (III), sabinene glycol (IV), sabinene ketone (V) and thujyl alcohol (VI).



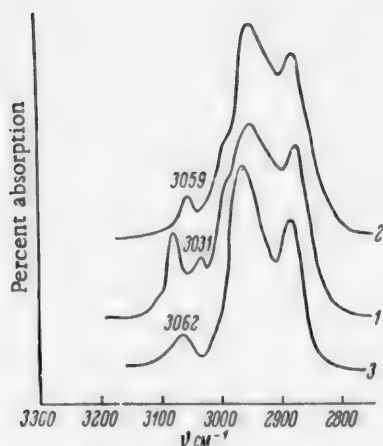


Fig. 1. Infrared absorption spectra in the region 3200-2800  $\text{cm}^{-1}$ . 1) Sabinene; 2) thujane; 3) sabinene ketone.

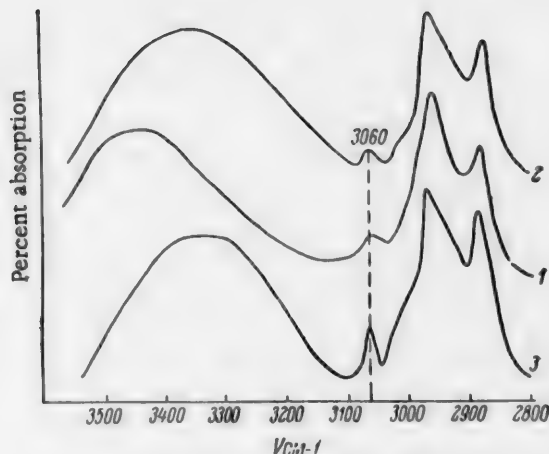


Fig. 2. Infrared absorption spectra in the region 3500-2800  $\text{cm}^{-1}$ . 1) Sabinene glycol monoacetate; 2) sabinene glycol; 3) thujyl alcohol.

The infrared spectra of all these compounds contained absorption bands in the region interesting us (3030-3060  $\text{cm}^{-1}$ ) (see Figs. 1 and 2.). Thus, the rule found by Cole was confirmed in the case of the bicyclic terpenes we investigated.

It is evident that the field of application of this rule should be restricted to compounds containing an unsubstituted  $\text{CH}_2$  group in the cyclopropane ring. Among bicyclic terpenes, this includes compounds which are derivatives of bicyclohexane-[0, 1, 3.].

It should be noted that in the spectrum of sabinene there is a strong displacement toward lower frequencies (by 30  $\text{cm}^{-1}$ ) of the absorption band characteristic of a  $\text{CH}_2$  group in a three-membered ring (Fig. 1, curve 1). This is probably connected with conjugation of the double bond with the cyclopropane ring. According to the data of Cole [2], the spectrum of  $\alpha$ -thujene, in whose molecule there is conjugation of a double bond with the cyclopropane ring, is also characterized by lower frequencies for the C-H valence vibrations in comparison with the spectrum of thujane.

#### EXPERIMENTAL

L-Sabinene (I) was isolated from wild carrots (*Daucus carota* L.). B. p. 50-50.5° at 15 mm,  $d_4^{20}$  0.8496,  $n_D^{20}$  1.4677,  $[\alpha]_D$  84.03°,  $\text{MR}_D$  44.47. Calc. 44.21.\*

Thujane (II) was obtained by hydrogenation of sabinene over Pt black in anhydrous alcohol. B. p. 59-60° at 28 mm  $d_4^{20}$  0.8208,  $n_D^{20}$  1.4440,  $[\alpha]_D$  -11.42,  $\text{MR}_D$  44.66. Calc. 44.62.

Sabinene glycol monoacetate (III) was isolated from the products of oxidation of L-sabinene with peracetic acid. B. p. 123-125° at 5 mm,  $d_4^{20}$  1.0352,  $n_D^{20}$  1.4686,  $[\alpha]_D$  -33.21°,  $\text{MR}_D$  57.06. Calc. 57.11.

Sabinene glycol (IV) was obtained by hydrolysis of sabinene glycol monoacetate. B. p. 135-136° at 6 mm,  $d_4^{20}$  1.0228,  $n_D^{20}$  1.4830,  $[\alpha]_D$  -40.2°,  $\text{MR}_D$  47.54. Calc. 47.97.

Sabinene ketone (V) was obtained by oxidation of sabinene glycol with lead tetracetate. B. p. 89.5-90° at 10 mm,  $d_4^{20}$  0.9555,  $n_D^{20}$  1.4682,  $[\alpha]_D$  + 22.4°,  $\text{MR}_D$  40.2. Calc. 40.08.

Thujyl alcohol (VI) (from the collection of L. A. Chugaev). B. p. 75.5-76° at 4 mm,  $d_4^{20}$  0.9187,  $n_D^{20}$  1.4590,  $[\alpha]_D$  + 116.1°,  $\text{MR}_D$  45.82. Calc. 45.50.

The infrared spectra were obtained with an IKS-11 spectrometer with an LiF prism; the slit width was 0.2 mm and the thickness of the layer of substance 9  $\mu$ .

\* In the calculation of the molecular refractions of all the compounds, allowance was made for the increment of the three-membered ring, equal to 0.71.

## SUMMARY

The infrared absorption spectra of the terpenes sabinene, sabinane (thujane), sabinene glycol monoacetate, sabinene glycol, sabinene ketone and thujyl alcohol contain an absorption band in the region of  $3030\text{--}3060\text{ cm}^{-1}$ , which is characteristic of a  $\text{CH}_2$  group in a three-membered ring. This confirms the data of Cole on the possibility of detecting a cyclopropane ring in complex molecules and, in particular, terpenes by infrared spectra.

Conjugation of a double bond with a cyclopropane ring apparently results in a reduction in the frequency of the C-H valence vibration in a  $\text{CH}_2$  group of a cyclopropane ring.

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## STUDIES ON BASES IN THE BARK OF *Hippophaë rhamnoides*

### I. ISOLATION OF 5-HYDROXYTRYPTAMINE (SEROTONINE)

M. F. Petrova and G. B. Men'shikov

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Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 7,

pp. 2413-2415, July, 1961

Original article submitted July 4, 1960

The "basic alkaloids" of this plant (belonging to the family Elaeagnaceae) are first mentioned in P. S. Masagotov's paper [1], but unfortunately neither the physical properties of the alkaloids nor the methods of their preparation are given. Our investigations were begun when it was found that aqueous and alcoholic extracts of this plant contain substances active against various types of experimental tumors in mice and rats [2]. Naturally, the question arose of the isolation of the active principle in a pure form.

The very first experiments revealed that the active principle is a base, since when active solutions were passed through cation- and anion-exchange resins, the active principle was retained only by the former and passed freely through the latter. However, attempts to isolate these bases by the usual methods employed for alkaloids (extraction from aqueous solutions by hydrophobic solvents) were not successful.

Only adsorption on cation-exchange resins followed by elution with hydrochloric acid yielded a mixture of hydrochlorides from which so far only one,  $C_{10}H_{12}N_2O \cdot HCl$  with  $R_f$  0.40, has been isolated in a pure form. The hydrochloride and the picrate and creatinine sulfate derivatives obtained from it were compared with the corresponding 5-hydroxytryptamine salts and found to be completely identical.

The content of 5-hydroxytryptamine in the dry bark varies from 0.3 to 0.4%, which is much more than in other plants [3]. To isolate 5-hydroxytryptamine, it was necessary to use a carboxylic acid cation-exchange resin, since although 5-hydroxytryptamine is also absorbed satisfactorily by a sulfonic acid resin, it cannot then be eluted with hydrochloric acid and caustic alkali has to be employed. When this is done, the eluate undergoes such strong resinification that the isolation of 5-hydroxytryptamine in a pure form becomes very difficult.

These bases do not give a color reaction with Dragendorff's reagent—a typical reagent for alkaloids. As these compounds are readily oxidized, we employed an alkaline potassium permanganate solution as developer for paper chromatography. In subsequent work we found that the chromatograms can also be developed with a solution of diazotized sulfanilic acid.

The paper chromatograms have shown that, apart from 5-hydroxytryptamine, the mixture of hydrochlorides contains two other bases, the chemical nature of which is so far unknown.

In conclusion, we thank A. D. Chinaeva for the microanalyses required for this work, which were carried out under her immediate supervision.

#### EXPERIMENTAL

Preparation of 5-Hydroxytryptamine. Ten kg of powdered air-dry bark of *Hippophaë rhamnoides* was subjected to exhaustive extraction with 0.5% hydrochloric acid. The extract was neutralized to pH 7 and the precipitated resinous residue was filtered off. The filtrate was acidified with hydrochloric acid to pH 5 and then passed through a column filled with KB-4n-2 cation-exchange resin previously treated with 5% sodium hydroxide solution and then thoroughly washed free of the excess of this reagent. The saturation of the column was followed by testing the solution passing through with silicotungstic acid. After saturation, the resin was washed with distilled water and the adsorbed products were eluted with 5% hydrochloric acid. The eluate was brought to pH 4 by means of sodium carbonate and evaporated in a vacuum (15 mm), in a stream of nitrogen, to half its volume. It was then separated from the

\* With the participation of P. S. Krants,

precipitated resin and evaporated to dryness under the same conditions. The dry solid residue was treated several times with hot anhydrous alcohol in an atmosphere of nitrogen, the alcoholic extracts were combined, and the solvent distilled off completely. The remaining solid amorphous brown mass consisted, according to paper chromatography, of three compounds with  $R_f$  0.25, 0.4 and 0.6. The solvent used for the chromatography was n-butyl alcohol-acetic acid-water (4:1:5, by volume). The chromatograms were developed either by means of an alkaline potassium permanganate solution or with a solution of diazotized sulfanilic acid.

The amorphous mass of the hydrochloride was dissolved in a very small volume of hot anhydrous alcohol acidified with hydrochloric acid. On standing at 0°, large lamellar crystals of 5-hydroxytryptamine hydrochloride separated from the solution. After two recrystallizations from anhydrous alcohol, the melting point was 163-165° and the  $R_f$  0.4 (for the same solvent as above). The yield of the hydrochloride was 0.3-0.4% of the weight of the bark (depending on the specimen).

A solution of the free base, obtained by adding to the hydrochloride solution the calculated quantity of hydrated silver oxide, was employed for the preparation of the picrate and a double salt with creatinine sulfate, a compound characteristic of 5-hydroxytryptamine [4]. The salts proved to be identical with those prepared from synthetic 5-hydroxytryptamine.

Apart from these already-known salts, the picrolonate, hitherto not described for 5-hydroxytryptamine, was also prepared. An aqueous solution of picrolonic acid was added to an aqueous solution of the base. The picrolonate separated as yellow needles melting, after recrystallization from water, at 222-223°.

Found %: C 54.18; H 4.87; N 18.96.  $C_{10}H_{12}ON_2 \cdot C_{10}H_8O_5N_4$ . Calculated %: C 54.51; H 4.59; N 19.09.

#### SUMMARY

1. 5-Hydroxytryptamine has been isolated from the bark of Hippophaë rhamnoides in 0.3-0.4% yield, based on the dry weight of the bark.
2. The presence of two other, hitherto unidentified, bases in the bark has been established.

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## STEREOCHEMICAL INVESTIGATIONS

### X. SCHIFF'S BASES FROM OPTICALLY ACTIVE 2-AMINO BUTANE

V. M. Potapov, A. P. Terent'ev, and S. P. Spivak

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Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 7,

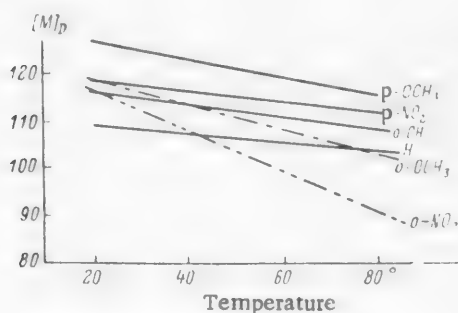
pp. 2415-2419, July, 1961

Original article submitted June 22, 1960

Continuing our studies on the optical rotation of Schiff's bases, we selected optically active 2-aminobutane as the starting material for the present work. The choice was made because 2-aminobutane is the simplest of the optically active amines. Its rotation is determined principally by the contribution of the amino-group absorption bands, whereas the rotation in the visible region of the spectrum of amines studied hitherto is due to the contributions of two adsorption bands—those of the amino group and of the aromatic nucleus.

The 2-aminobutane was synthesized by the reductive amination of methyl ethyl ketone by Leuckart's method [1], with the subsequent separation of the racemic amine by means of (+)-tartaric acid in aqueous solution. The maximum rotation of the amine found,  $[\alpha]_D^{20} + 8.1^\circ$ , is somewhat higher than the published values [2].

Resolution of 2-aminobutane by means of tartaric acid takes a long time and does not always give reliable results. Consequently, we attempted to use other asymmetric acid reagents. The attempt to resolve 2-aminobutane with dibenzoyl tartaric acid in water, methanol, or acetone was unsuccessful. Resolution by means of (-)-menthylsulfuric acid yields the amine with a specific rotation of  $1^\circ$  after three recrystallizations. The resolution by means of menthylsulfuric acid should nevertheless be achieved more rapidly than that described by Pope and Gibson [3] using  $\alpha$ -bromocamphorsulfonic acid, which required 27 (!) recrystallizations.



Temperature dependence of molar rotation in butanol.

The published data for the boiling point of 2-aminobutane are extremely contradictory (between 61 and 70°), apparently as a result of the ability of the amine to give stable molecular compounds with water [4]. For this reason, we distilled the amine using a column with an effectiveness of 15 theoretical plates and obtained a boiling point of 61.7° at 744 mm.

By allowing the optically active 2-aminobutane to react with aromatic aldehydes, 11 Schiff's bases were prepared, and their optical rotation in various solvents was measured. The physical constants of the Schiff's bases obtained are given in the experimental part, and the optical activities in Table 1. The temperature dependence of the rotation of some of the bases has also been measured (see figure).

The effect of substituents on the rotation of Schiff's bases from 2-aminobutane is in general small, not exceeding the effect of solvent and temperature. The order in which the values of the rotation increase in the series of Schiff's bases from 2-aminobutane differs from that observed for the Schiff's bases studied previously. Furthermore, this order varies for different solvents, as was observed in the previous work.

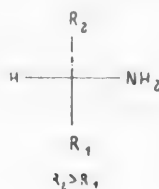
In one of our previous papers [5] we suggested that there may be a parallelism between the rotation of Schiff's bases and the effect of acids on the rotation of the corresponding amines. It appeared reasonable to suppose that the greater the role of the amino group in the rotation, the more should the latter alter after changes involving the amino group, in particular the formation of salts or Schiff's bases. If this were correct, the sign of the rotation of 2-amino-butane, which exhibits a marked "acid effect," should be reversed after formation of Schiff's bases. However,

measurements have shown that the rotation of Schiff's bases from 2-aminobutane is of the same sign as that of the initial amine. To find to what extent the "acid effect" for 2-aminobutane depends on the solvent and concentration, we have measured the rotation of the amine hydrochloride in water and methanol at various concentrations. It is evident from the data in Table 2 that the dependence of the specific rotation on concentration is considerable.

TABLE 1  
Molecular Rotation  $[M]_D^{20}$  of Schiff's Bases from (+)-2-Aminobutane

Aldehyde	Solvent						
	without solvent	benzene	methanol	acetone	dichloroethane	heptane	butanol
Furfural	+ 84.7°	+ 70.6°	+ 105.5°	+ 99.9°	—	+ 99.5°	—
o-Methoxybenzaldehyde	+106.2	+ 82.7	+ 98.7	+104.3	+ 75.3	+ 98.2	+118°
Benzaldehyde	+132.6	+ 83.9	+140.3	+116.4	+112.3	+ 57.7	+110
p-Dimethylaminobenzaldehyde	+104.2	+ 91.2	+137.9	+144.5	+136.5	+113.5	—
Salicylic aldehyde	+110.2	+ 92.6	+145.2	+116.4	+125.1	+115	+118
Anisic aldehyde	+119.4	+ 94.9	+142.8	+127	+122.4	+119.7	+128
p-Chlorobenzaldehyde	+121.3	+ 98.5	+127.4	+124.7	+ 97.3	+127.1	—
B-Hydroxynaphthaldehyde	—	+100.5	+174.3	+145.5	+172.6	+ 85.2	—
p-Nitrobenzaldehyde	+140.0	+107.7	+144.8	+140.9	+109.7	+131	+128
p-Hydroxybenzaldehyde	—	+110.8	+114.1	+108.4	+106.1	—	—
o-Nitrobenzaldehyde	+121.0	+139.0	+135.9	+115.8	+ 92.7	+148.9	+126

Comparison of the results obtained so far for  $\alpha$ -phenylethylamine (I) and its analogs (II, III),  $\alpha$ -benzylethylamine (IV) and 2-aminobutane (V), with respect to their configuration, represented by the projection formulae below, reveals that the sign of the rotation of Schiff's bases derived from amines of the same configuration (but not with the same sign of rotation!) is the same: Amines with the configuration shown below give levorotatory Schiff's bases with aromatic aldehydes not containing ortho-substituents.



(+)-(I)	( $R_1 = CH_3$ ;	$R_2 = C_6H_5$ )
(+)-(II)	( $R_1 = CH_3$ ,	$R_2 = C_6H_5(CH_2)_2$ )
(+)-(III)	( $R_1 = C_2H_5$ ,	$R_2 = C_6H_5$ )
(-)-(IV)	( $R_1 = CH_3$ ,	$R_2 = CH_2C_6H_5$ )
(-)-(V)	( $R_1 = CH_3$ ,	$R_2 = C_2H_5$ )

This is apparently due to the fact that the adsorption band of the azomethine link makes a decisive contribution to the rotation of Schiff's bases.

TABLE 2  
Molecular Rotation of (+)-2-Aminobutane Hydrochloride in Water

Water		Methanol	
Concentration, %	$[M]_D$	Concentration, %	$[M]_D$
6.5	-4.69°	9.36	-1.14°
3.25	-3.37	3.96	-0.96
1.62	-2.37	1.98	-0.41

It should be noted that the figure again clearly reveals the frequently observed peculiar position of the ortho-substituted Schiff's bases, reflected in the present case in the higher temperature coefficient for the o-nitro-derivative.

#### EXPERIMENTAL

**2-Aminobutane.** The synthesis and resolution into optical antipodes were carried out as described previously [6]. The hydrochloride of the (+)-amine has m. p. 144-145° (published value 143° [7]). The optical rotation was measured in a 2 dm tube.

Benzylidene-(+)-2-aminobutane. Benzaldehyde (0.027 mole) was dissolved in 20 ml of benzene, treated with 0.027 mole of (+)-2-aminobutane, and refluxed for 1 hr. The benzene was then distilled off and the residual oil was twice distilled in a vacuum.

Yield 72%, b. p. 89-91° at 7 mm,  $d_4^{20}$  0.9189,  $n_D^{20}$  1.5221,  $MR_D$  54.75; calc. 53.35.\* Published data for the racemate [9]: b. p. 86-88° at 3 mm,  $n_D^{20}$  1.5211.

Found %: N 7.30,  $C_{11}H_{15}N$ . Calculated %: N 7.15.

All the Schiff's bases listed below were prepared similarly.

o-Methoxybenzylidene-(+)-2-aminobutane.

Yield 66.4%, b. p. 126-128° at 10 mm,  $d_4^{20}$  0.9876,  $n_D^{20}$  1.5350,  $MR_D$  60.29; calc. 59.76.

Found, %: N. 7.53,  $C_{12}H_{17}ON$ . Calculated %: N 7.32.

p-Dimethylaminobenzylidene-(+)-2-aminobutane.

Yield 83%, b. p. 156-158° at 7 mm,  $d_4^{20}$  0.9691,  $n_D^{20}$  1.5045,  $MR_D$  71.6; calc. 67.92.

Found %: N 13.30,  $C_{13}H_{20}N_2$ . Calculated %: N 13.21.

p-Hydroxybenzylidene-(+)-2-aminobutane.

Yield 50%, b. p. 170-174° at 10 mm; a vitreous mass for which neither the density nor the refractive index could be determined.

Found %: N 7.80,  $C_{11}H_{15}ON$ . Calculated %: N 7.90.

o-Hydroxybenzylidene-(+)-2-aminobutane.

Yield 56%, b. p. 116° at 7 mm,  $d_4^{20}$  0.9980,  $n_D^{20}$  1.5435,  $MR_D$  56.01; calc. 54.97.

Found %: N 7.77,  $C_{11}H_{15}ON$ . Calculated %: N 7.90.

Furfurylidene-(+)-2-aminobutane.

Yield 50%, b. p. 76° at 8 mm,  $d_4^{20}$  0.985,  $n_D^{20}$  1.5057,  $MR_D$  45.59; calc. 46.20.

Found %: N 8.90,  $C_9H_{13}ON$ . Calculated: N 9.26.

$\beta$ -Hydroxynaphthylmethylene-(+)-2-aminobutane.

Yield 60.3%, b. p. 193° at 8 mm,  $d_4^{20}$  1.1087.

Found %: N 6.27,  $C_{15}H_{17}ON$ . Calculated %: N 6.20.

Methoxybenzylidene-(+)-2-aminobutane.

Yield 68.2%, b. p. 132° at 7 mm,  $d_4^{20}$  0.9875,  $n_D^{20}$  1.5395,  $MR_D$  60.73; calc. 59.76.

Found %: N 7.51,  $C_{12}H_{17}ON$ . Calculated %: N 7.32.

p-Nitrobenzylidene-(+)-2-aminobutane.

Yield 37.7%, b. p. 150-151° at 7 mm,  $d_4^{20}$  1.079,  $n_D^{20}$  1.5537,  $MR_D$  61.21; calc. 59.04.

Found %: N 13.34,  $C_{11}H_{14}O_2N_2$ . Calculated %: N 13.58.

o-Nitrobenzylidene-(+)-2-aminobutane.

Yield 74.9%, b. p. 142-143° at 8 mm,  $d_4^{20}$  1.074,  $n_D^{20}$  1.5396,  $MR_D$  60.2; calc. 59.04.

Found %: N 13.50,  $C_{11}H_{14}O_2N_2$ . Calculated %: 13.58.

\* According to data in the literature, the molecular refractions of Schiff's bases differ markedly from the calculated values [8].

p-Chlorobenzylidene-(+)-2-aminobutane.

Yield 70%, b. p. 113-116° at 7 mm,  $d_4^{20}$  1.0395,  $n_D^{20}$  1.5401,  $M_R^D$  59.04; calc. 58.17.

Found %: N 7.30.  $C_{11}H_{14}NCl$ . Calculated %: N 7.16.

SUMMARY

Eleven Schiff's bases have been prepared from optically active 2-aminobutane. Their optical rotation in various solvents and the temperature dependence of the rotation have been determined.

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# B-ALKOXYETHYLISOPROPYLMALONIC ESTERS

A. V. Bogatskii and N. A. Goryachuk

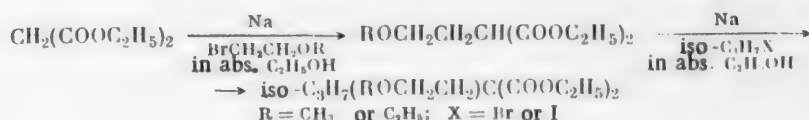
I. I. Mechnikov Odessa State University

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Original article submitted June 26, 1960

In the course of work on the synthesis of alkoxyethylalkylmalonic esters and an investigation of their properties, we obtained  $\beta$ -methoxyethylisopropylmalonic and  $\beta$ -ethoxyethylisopropylmalonic esters (not described previously) as follows:

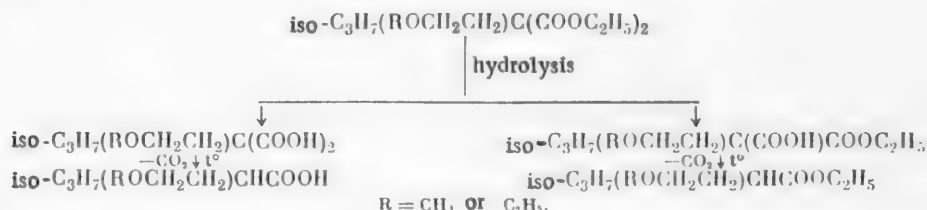


Investigation of the mechanism of the synthesis of these compounds has revealed that when the reaction is carried out in anhydrous alcohol,  $\beta$ -alkoxyethylisopropylmalonic esters are formed only when the alkoxyethyl radical is introduced into the malonic ester molecule first, followed by the isopropyl radical, and not the reverse.

This is consistent with the lower reactivity of malonic esters monosubstituted with secondary radicals toward alkylation with halogen derivatives in alcohol in the presence of sodium ethoxide [1-10] due to the lower "acidity" of the methylene hydrogen and the presence of steric hindrance. A number of workers [8-10] have shown that this difficulty can be overcome by carrying out the alkylation in the presence of sodium tert-butoxide in tert-butyl alcohol. On alkylating the isopropylmalonic ester with  $\beta$ -methoxyethyl bromide in this way we obtained  $\beta$ -methoxyethylisopropylmalonic ester, but only in 12% yield.

We have investigated some of the chemical properties of  $\beta$ -alkoxyethylisopropylmalonic esters. Their hydrolysis yielded  $\beta$ -methoxyethylisopropylmalonic and  $\beta$ -ethoxyethylisopropylmalonic acids, which have not so far been described. The decarboxylation of these acids gave  $\gamma$ -methoxy- $\alpha$ -isopropylbutyric and  $\gamma$ -ethoxy- $\alpha$ -isopropylbutyric acids, which have not been described either.

Even after prolonged heating (10 hr) with aqueous-alcoholic potassium hydroxide, the hydrolysis of the initial esters is incomplete. The reaction product consists of a mixture of the corresponding dicarboxylic acid and its monoethyl ester. On decarboxylation, this mixture gives not only the corresponding  $\gamma$ -alkoxy- $\alpha$ -isopropylbutyric acids, but also their ethyl esters:



The reason for this type of reaction may be steric hindrance due to the screening effect of the isopropyl and alkoxyethyl radicals.

## EXPERIMENTAL

Malonic ester had b. p. 58° (2.5 mm),  $n_D^{20}$  1.4141; isopropyl bromide—b.p. 59-61°,  $n_D^{20}$  1.4285; isopropyl iodide—b. p. 89-91°,  $n_D^{20}$  1.5028; 1-bromo-2-methoxyethane, prepared by a method analogous to that described by Harrison and Dill [11], had b. p. 110-114°,  $n_D^{20}$  1.4450; 1-bromo-2-ethoxyethane, also prepared according to Harrison and Dill [11], had b. p. 125-127°,  $n_D^{20}$  1.4250.

**$\beta$ -Methoxyethylmalonic Ester.** A solution of sodium alcoholate, prepared from 50.6 g of sodium in 800 ml of anhydrous alcohol, was treated with 704 g of malonic ester and then with 306 g of 1-bromo-2-methoxyethane. Double the required quantity of malonic ester was used (after Leuchs [12]) in order to prevent the formation of the disubstituted malonic ester. The reaction mixture was refluxed on an oil bath for 4 hr at 110°, until neutral. The major part of the alcohol was then distilled off, the residue poured into water, the ester layer separated, and the aqueous layer three times extracted with ether; the ethereal extracts were combined and dried over calcium chloride; the ether was then distilled off and the reaction product fractionated in a vacuum. After the removal of the excess of malonic ester by distillation, the  $\beta$ -methoxyethylmalonic ester was distilled. Yield 275 g (57.3%). The ester is a colorless liquid with a faint smell.

B. p. 85-87° at 3 mm,  $d_4^{20}$  1.0434,  $n_D^{20}$  1.4252,  $M_R D$  53.44; calc. 53.33.

Found %: C 54.99; H 8.35,  $C_{10}H_{18}O_5$ . Calculated %: C 55.05; H 8.25.

**$\beta$ -Ethoxyethylmalonic Ester.** This was prepared similarly as  $\beta$ -methoxyethylmalonic ester; yield 72%. It was synthesized previously in very much smaller yield [13].

B. p. 108-111° at 4 mm,  $d_4^{20}$  1.0249,  $n_D^{20}$  1.4258,  $M_R D$  57.99; calc. 57.95.

**$\beta$ -Alkoxyethylisopropylmalonic Ester.\*** A solution of sodium alcoholate, prepared from 23 g of sodium in 400 ml of anhydrous ethyl alcohol, was treated with 218 g of  $\beta$ -methoxyethylmalonic (or with 232 g of  $\beta$ -ethoxyethylmalonic) ester and then with 170 g of isopropyl iodide. The reaction mixture was heated on an oil bath at 110° for 6 hr, until neutral, after which the product was isolated as described above. When the ether had been distilled off, the product was fractionated in a vacuum. Initially, the unreacted  $\beta$ -methoxyethylmalonic (or  $\beta$ -ethoxyethylmalonic) ester distilled off, and then the  $\beta$ -alkoxyethylisopropylmalonic esters, the properties of which are described in Table 1.

The reaction with isopropyl bromide under the same conditions gave a yield of only 58.6%, even after heating for 70 hr.

On carrying out the reaction by Verrier's method [8] in trimethylcarbinol, the  $\beta$ -methoxyethylisopropylmalonic ester (b.p. 104° at 3 mm,  $d_4^{20}$  1.0129,  $n_D^{20}$  1.4370) was obtained in 12% yield.

**Hydrolysis of  $\beta$ -Alkoxyethylisopropylmalonic Esters.** The esters were hydrolyzed by heating with 10% aqueous-alcoholic potassium hydroxide solution for 10 hr; the extract was then diluted with water, the alcohol completely distilled off, and the residue, after acidification with sulfuric acid, extracted with ether. The ethereal extracts were dried with calcium chloride and the ether was carefully removed by distillation. According to the neutralization numbers of the hydrolysis products [14], the resulting thick oil is a mixture of  $\beta$ -alkoxyethylisopropylmalonic acids and their monoethyl esters (Table 2).

We have succeeded in isolating the dicarboxylic acids from this mixture by alkaline extraction using the differences in the dissociation constants of the acids and the acid esters [10]. After recrystallization from benzene, the physical constants of the acids were determined (Table 3).

The monoethyl esters of  $\beta$ -alkoxyethylisopropylmalonic acids could not be isolated in a pure state because of their very great tendency toward decarboxylation.

**Decarboxylation of Hydrolysis Products.** The mixture obtained on hydrolysis was decarboxylated by heating on an oil bath at 140-160° until evolution of carbon dioxide ceased. The resulting mixture of  $\gamma$ -alkoxy- $\alpha$ -isopropylbutyric acids and their ethyl esters was fractionated in a vacuum. The proportions of the mixture components are given in Table 2. The physical properties of  $\gamma$ -alkoxy- $\alpha$ -isopropylbutyric acids are set out in Table 4. The ethyl esters of  $\gamma$ -alkoxy- $\alpha$ -isopropylbutyric acids were also synthesized (in 90% yield) by the esterification (heating for

\*S. G. Golentovskaya took part in the synthesis of  $\beta$ -ethoxyethylisopropylmalonic ester.

TABLE 1.  $\beta$ -Alkoxyethylisopropylmalonic Esters  $\text{iso-C}_3\text{H}_7(\text{ROCH}_2\text{CH}_2)\text{C}(\text{COOC}_2\text{H}_5)_2$ 

R	Yield, %	B. p. (pressure in mm)	$d_4^{20}$	$n_D^{20}$	MR <sub>D</sub>		Empirical formula	%C		%H	
					Found	Calc.		Found	Calc.	Found	Calc.
CH <sub>3</sub>	75.5	101–102° (3)	1.0112	1.4360	67.21	67.19	C <sub>13</sub> H <sub>24</sub> O <sub>5</sub>	59.94	59.97	9.23	9.29
C <sub>2</sub> H <sub>5</sub>	75.0	117–118 (4)	1.0006	1.4365	71.80	71.70	C <sub>14</sub> H <sub>26</sub> O <sub>5</sub>	61.48	61.70	9.73	9.70

TABLE 2. Neutralization Numbers of the Esters  $\text{iso-C}_3\text{H}_7(\text{ROCH}_2\text{CH}_2)\text{C}(\text{COOC}_2\text{H}_5)_2$ 

Neutralization number					Mixture composition, %	
R	Found	Calc.			Dicarboxylic acids	Acid esters of dicarboxylic acids
		For dicarboxylic acids	For acid esters of dicarboxylic acids			
CH <sub>3</sub>	366	549	241		43.48	56.52
C <sub>2</sub> H <sub>5</sub>	353	516	228		58.14	41.48

TABLE 3.  $\beta$ -Alkoxyethylisopropylmalonic Acids  $\text{iso-C}_3\text{H}_7(\text{ROCH}_2\text{CH}_2)\text{C}(\text{COOH})_2$ 

R	M.p.	Neutralization number		Empirical formula	%C		%H	
		Found	Calc.		Found	Calc.	Found	Calc.
CH <sub>3</sub>	82–83°	546	549	C <sub>9</sub> H <sub>16</sub> O <sub>5</sub>	52.62	52.93	8.03	7.90
C <sub>2</sub> H <sub>5</sub>	101–103	507	516	C <sub>10</sub> H <sub>18</sub> O <sub>5</sub>	55.25	55.03	8.58	8.31

TABLE 4.  $\gamma$ -Alkoxy- $\alpha$ -isopropylbutyric Acids  $\text{ROCH}_2\text{CH}_2\text{CH}(\text{iso-C}_3\text{H}_7)\text{COOH}$ 

R	B.p. (pressure in mm)	$d_4^{20}$	$n_D^{20}$	MR <sub>D</sub>		Empirical formula	%C		%H	
				Found	Calc.		Found	Calc.	Found	Calc.
CH <sub>3</sub>	89–91° (0.5)	0.9901	1.4361	42.26	42.32	C <sub>8</sub> H <sub>16</sub> O <sub>3</sub>	59.98	59.97	10.03	10.06
C <sub>2</sub> H <sub>5</sub>	91–93 (0.5)	0.9695	1.4360	46.93	46.94	C <sub>9</sub> H <sub>18</sub> O <sub>3</sub>	62.01	62.07	10.53	10.34



TABLE 5. Comparison of the Properties of the Ethyl Esters of  $\gamma$ -Methoxy- $\alpha$ -isopropylbutyric Acid (Ia) and  $\gamma$ -Ethoxy- $\alpha$ -isopropylbutyric Acid (IIa) Prepared by the Decarboxylation of the Hydrolysis Products with the Properties of the Corresponding Esters [(Ib) and (IIb)] Obtained by Synthesis

Ester	B.p. (pressure in mm)	$d_4^{20}$	$n_D^{20}$	Saponification no.		% C		% H	
				found	calc.	found	calc.	found	calc.
(Ia)	54—55° (1)	0.9263	1.4218	299.9		63.89		10.59	
(Ib)	50 (0.8)	0.9270	1.4218	300.4	298.4	63.63	63.83	10.85	10.64
(IIa)	54 (0.5)	0.9152	1.4222	279.2		65.02		10.91	
(IIb)	62 (1.5)	0.9152	1.4222	277.1	277.8	65.54	65.34	10.90	10.89

4 hr) of the corresponding acids (0.33 mole) with anhydrous alcohol (150 ml) in the presence of concentrated sulfuric acid (15 ml). The properties of the ethyl esters prepared by the decarboxylation [(Ia) and (IIa)] were compared with those obtained synthetically [(Ib) and (IIb)] and their identity was confirmed (see Table 5). The esters, like the acids, have not been described before.

The subject of the present work was suggested by V. P. Gol'mov.

#### SUMMARY

1.  $\beta$ -Methoxyethylmalonic,  $\beta$ -methoxyethylisopropylmalonic and  $\beta$ -ethoxyethylisopropylmalonic esters (previously not described) have been compared.

2. In the synthesis of  $\beta$ -alkoxyethylisopropylmalonic esters in anhydrous alcohol, the alkoxyethyl radical must be introduced into the malonic ester molecule first, before the isopropyl radical. The radicals may be introduced in the reverse order when the reaction is carried out in anhydrous tert-butyl alcohol.

3. It has been shown that hydrolysis of  $\beta$ -alkoxyethylisopropylmalonic esters leads to the formation of a mixture of  $\beta$ -alkoxyethylisopropylmalonic acids and their monoethyl esters; this is due to steric hindrance of the hydrolysis caused by the screening effect of the isopropyl and alkoxyethyl radicals. Decarboxylation of the mixture yields  $\gamma$ -alkoxy- $\alpha$ -isopropylbutyric acids and their ethyl esters.

4. The physical properties of  $\beta$ -methoxyethylisopropylmalonic,  $\beta$ -ethoxyethylisopropylmalonic,  $\gamma$ -methoxy- $\alpha$ -isopropylbutyric, and  $\gamma$ -ethoxy- $\alpha$ -isopropylbutyric acids and those of the ethyl esters of the  $\gamma$ -alkoxy- $\alpha$ -isopropylbutyric acids (all described for the first time) are given.

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## GLUCOSIDES OF *Adonis* SPECIES

### I. GLUCOSIDES OF *Adonis chrysocyathus* Hook f. et Thom.

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Among plants of the *Adonis* species, *A. vernalis* L. is best known because of its wide use in medicine. The extracts of this plant have been found to contain cymarin [1] and adonitoxin [2-4]. Recently cymarin and strophanthidin [5] have been isolated from the plant native to the U.S.S.R. Cymarin has also been found in the roots of *A. amurensis* L. of Japanese origin [6].

We have investigated the steroid glucosides of *Adonis chrysocyathus* Hook. f. et. Thom. N. A. Kambulin and T. G. Sultanov [7] first noted the considerable content of cardiotonic substances (detected biologically) in this plant. The plants were gathered toward the end of their period of flowering, at the beginning of fructification, on the northern slopes of Kungei-Alatau ridge in the upper reaches of the Aktash-Koroo river (Chon-Kemin basin) in July, 1958. The biological activity (per gram of the air-dry starting material) of the aerial parts of the plant was 80, and the activity of the roots 304, frog heart units.

Our earlier communication [8] concerned the presence of cymarin in *A. chrysocyathus*. To facilitate the isolation of this glucoside, the plant roots were subjected to preliminary fermentation.

The present paper describes a method by means of which a mixture of glucosides can be separated without their preliminary hydrolysis. As a result, apart from cymarin, we have detected in the plant K-strophanthin- $\beta$  [9, 10], the sole source of which used to be the seeds of *Strophanthus kombe* Oliv. (recently it has also been found in *Apocynum androsaemifolium* L. and *Apocynum cannabinum* [11]). The yield of the glucosides from the roots of *A. chrysocyathus* was 0.105% of cymarin and 0.086% of K-strophanthin- $\beta$ . The K-strophanthin- $\beta$  from *A. chrysocyathus* was identified by comparing its physicochemical properties and those of its tetraacetate with the physicochemical properties of an authentic specimen of K-strophanthin- $\beta$  from *S. kombe* by means of elemental analysis, by color reactions, by paper chromatography ( $R_f$  value) and by the determination of its cardiotonic activity.

As already pointed out [11], the simultaneous occurrence of cymarin and K-strophanthin- $\beta$  is quite natural. Apart from the small group of glucosides of the *Digitalis* species and certain others, the majority of steroid glucosides are built up as follows:

aglucon + hexamethylose + D-glucose + D-glucose.

Because these glucosides play a major physiological role in vital processes, they are present in plants in a dynamic state of continuous breakdown and synthesis, as a result of which the plant may simultaneously contain mono-, di-, tri- and polyglucosides. In this case we obviously have the following equilibrium:

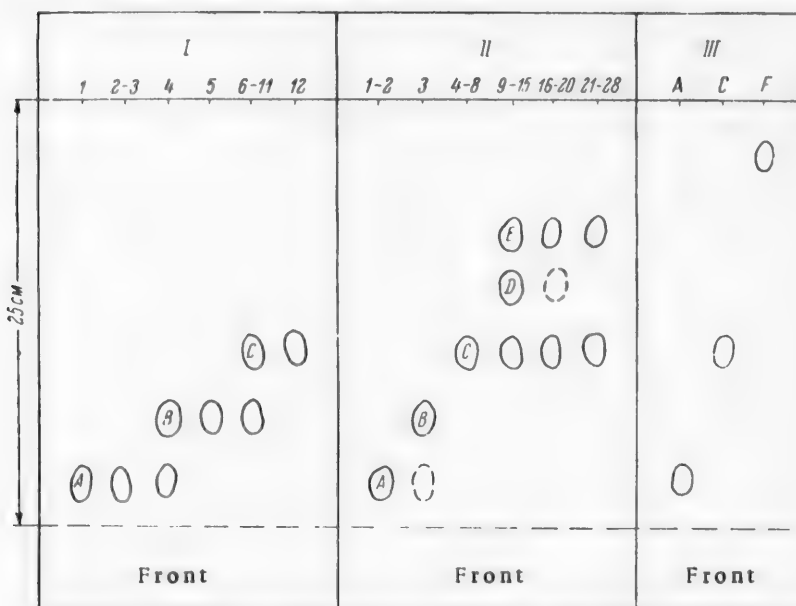
cymarin + D-glucose  $\rightleftharpoons$  K-strophanthin- $\beta$ .

Under certain conditions the equilibrium may be displaced by plant carbohydrases in either direction. It is also possible that K-strophanthoside, the triglucoside in this series, may also participate in this equilibrium, although in our experiments it was not detected.

The authors thank K. Isakov (Institute of Botany, Academy of Sciences, Kirgiz S.S.R.), who pointed out the location of the plants; N. A. Kambulin and T. G. Sultanov (Tashkent Medical Institute), who carried out the biological tests; and Prof. T. Reichstein (Basel, Switzerland), who kindly supplied authentic specimens of K-strophanthin- $\beta$  and K-strophanthoside.

Chromatography of the Glucoside Mixture from *Adonis chrysocyathus*

Fraction no.	Weight of dry residue, g	Appearance of product isolated	Spots on paper chromatogram (see figure)
Chloroform extract			
1	3.06	Crystalline mass	A
2-3	14.88	Pale yellow amorphous powder	A
4	2.68	"	A, B
5	1.65	"	B,
6-11	1.89	"	B, C
12	0.08	Brown amorphous mass	C
Chloroform-ethanol extract			
1-2	2.28	Crystalline mass	A
3	3.21	Pale yellow amorphous powder	(A), B
4-8	2.70	Crystalline K-strophanthin- $\beta$	C
9-15	0.91	Brown amorphous powder	C, D, E
16-20	1.11	Yellow amorphous powder	C, (D), E
21-28	0.92	"	C, E



Paper chromatograms. I) Chloroform extract; II) chloroform-ethanol extract; III) pure glucosides. A) Cymarín; C) K-strophanthin- $\beta$ ; F) K-strophanthoside.

#### EXPERIMENTAL

**Isolation and Separation of Glucosides.** Powdered roots of *A. chrysocyathus* (2.8 kg) were extracted five times by 90% ethanol with heating on a water bath. The combined ethanol extract was evaporated in a vacuum at 45-50° to a volume of 2 liters. The ballast materials were precipitated with a solution of 25 g of lead acetate in 50 ml of water. The precipitate was separated and washed on the filter with small portions of ethanol, and the wash solutions were combined with the main bulk of the extract. The excess of lead ions was precipitated with an aqueous solution of sodium sulfate and the lead sulfate precipitate was filtered off and also washed with ethanol. After repeated evaporation, the purified aqueous-ethanol extract (2.2 liters) was successively extracted with ether (3 × 600 ml), chloroform (3 × 700 ml), and with a mixture of chloroform and ethanol in 2:1 ratio (2 × 2 liters). After this, the aqueous

extract did not contain any more glucoside and was rejected. After distilling off the solvents and drying, the following quantities of dry residue were obtained: 20 g from the ether fraction, 29 g from the chloroform fraction and 23 g from the chloroform-ethanol fraction.

The ether fraction contained a very small quantity of glucoside and was not further investigated.

The dry extract from the chloroform fraction (29 g) was mixed with 45 g of aluminum oxide ("for chromatography") and introduced into the upper part of a column filled with 600 g of aluminum oxide. Similarly, 23 g of the chloroform-ethanol fraction was mixed with 30 g of aluminum oxide and also placed in a column containing 600 g of aluminum oxide. The glucosides in both columns were eluted with a mixture of equal volumes of toluene and butanol previously saturated with water. The fractions taken (each 1.5 liters in volume) were evaporated in a vacuum and analyzed by paper chromatography using [toluene-butanol (1:1)]-water as solvent; Raymond's reagent was used as developer. Fractions showing the same distribution of spots were combined. The characteristics of the separate fractions are given in the table and the paper chromatograms in the figure.

Since the fractions were analyzed with only one solvent, single spots do not represent in all cases pure compounds. Thus, the heaviest fractions (2 and 3) from the chloroform extract give several spots with the [benzene-chloroform (1:1)]-formamide solvent. These fractions were not investigated in detail.

Cymarín. The dry residues from fraction 1 of the chloroform extract and fractions 1 and 2 from the chloroform-ethanol extract were ground with methanol. A finely crystalline precipitate of cymarín (2.44 and 0.52 g, respectively; total, 2.96 g) was obtained. The crude cymarín was recrystallized from methanol: m. p. 142-144°,  $[\alpha]_D^{25} + 36.8^\circ \pm 1.5^\circ$  (c 1.52, ethanol). A sample mixed with cymarín isolated from Apocynum androsaemifolium [11] melted at 144-146° C. The Keller-Kiliani and Webb-Levi [12, 13] tests were positive.

Found %: C 64.37, 64.39; H 8.42, 8.55; OCH<sub>3</sub> 10.45, 10.28. C<sub>30</sub>H<sub>44</sub>O<sub>9</sub> · CH<sub>3</sub>OH. Calculated %: C 64.12; H 8.33; 2 OCH<sub>3</sub> 10.69.

K-Strophanthin-β. The residue from fractions 4-8 of the chloroform-ethanol extract was stirred with 2 ml of ethanol. A crystalline substance (2.42 g) melting at 190-192° was obtained. K-Strophanthin-β evidently exists in several polymorphic forms. The material obtained by recrystallization from 50% ethanol and dried in a vacuum desiccator melted at 194-196°, that recrystallized from 96% ethanol melted at 211-213° and had  $[\alpha]_D^{20} + 31.3 \pm 2^\circ$  (c = 1.51, methanol), and the product recrystallized from an ethanol-ether mixture melted at 229-230° and 234-235°. On recrystallization from 50% ethanol, the high-melting material melted at 194-196°. Stoll and co-workers [10] found for K-strophanthin-β recrystallized from water and from aqueous alcohol m. p. 195°,  $[\alpha]_D^{20} + 31.8^\circ$  (in methanol), and noted that the melting point varies depending on the way in which the sample is heated. The specimen of the glucoside from Strophanthus kombe supplied by T. Reichstein melted at 202-203°. In our experiments the analyses for all three polymorphic modifications were too low and indicated the presence of solvent of crystallization. The analysis of material obtained by recrystallization from 96% ethanol is given below.

Found % C 58.34, 58.22; H 8.01, 8.04; OCH<sub>3</sub> 4.83, 4.58. C<sub>36</sub>H<sub>54</sub>O<sub>14</sub> · H<sub>2</sub>O. Calculated %: C 59.33; H 7.74; OCH<sub>3</sub> 4.26. C<sub>36</sub>H<sub>54</sub>O<sub>14</sub> · 2H<sub>2</sub>O. Calculated %: C 57.90; H 7.83; OCH<sub>3</sub> 4.16.

The glucoside gives an emerald green color with 84% sulfuric acid. The Keller-Kiliani test gave a negative result, but the Webb-Levi [12, 13] test was positive. K-Strophanthin-β from three different plant sources—Strophanthus kombe, Apocynum androsaemifolium and Adonis chrysocyathus—exhibits the same R<sub>f</sub> value on paper chromatography using [toluene-butanol (1:1)]-water as solvent. The median lethal dose of K-strophanthin-β from Adonis chrysocyathus is 0.128 mg/kg (from tests on cats).

Tetra-O-Acetyl-K-Strophanthin-β. K-Strophanthin-β (0.25 g), 6 ml of dry pyridine and 4 ml of acetic anhydride were heated for 3 hr at 100°. After the usual treatment, 0.23 g of a crystalline substance was obtained; this had a melting point of 169-170° after recrystallization from ethanol.

Found %: C 58.29, 58.34; H 7.41, 7.33. C<sub>44</sub>H<sub>62</sub>O<sub>18</sub> · H<sub>2</sub>O. Calculated %: C 58.92; H 7.19.

#### SUMMARY

A complex mixture of glucosides, including cymarín and K-strophanthin-β, was isolated from the roots of Adonis chrysocyathus.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.*

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STUDIES ON ALKALOIDS OF THE C<sub>15</sub> SERIESVII. NEW ALKALOIDS FROM *Sophora pachycarpa*\*

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The previous papers [1,2] concerned new methods for the isolation of matrine, sophocarpine, and their N-oxides from vat residues in the manufacture of pachycarpine at the Chimkent Chemico-Pharmaceutical Plant, as well as sophocarpinols and esters of matrinic acid.

TABLE 1. Derivatives of the New Bases from the Non-Distilling Fraction of the Vat Residues from *Sophora pachycarpa*

Base	Derivative	M.p.	Analytical data, %	
			Found	Calc.
Base No. 1	Picrate	230° (decomp.)	N 14.89, 14.81	14.73
	Hydrochloride	340-342	Cl 12.94, 12.80	12.92
	Hydrobromide	380-382	Br 23.62, 24.44	23.46
	Hydroiodide	350-351	I 34.54, 33.69	34.00
	Iodomethylate	370-372	I 32.80, 32.78	32.73
Base No. 2 (goebeline)	Picrate	217-218 (decomp.)	N 14.4, 14.18	14.73
	Dihydrochloride	346-348	Cl 21.94, 21.90	21.98
	Hydrobromide	360-362	Br 24.44, 24.48	24.46
	Hydroiodide	359-360	I 33.74, 33.70	33.95
	Perchlorate	310	—	—
	Iodomethylate	344-345	I 32.81, 32.93	32.73

A number of methods for the isolation of alkaloids from *Sophora pachycarpa* are described in the literature [3-6]; a method for the isolation of sophocarpine from vat residues by means of ammonium chloride is also known [7].

In the course of further work on the distilling fraction of the vat residues accumulating in the manufacture of pachycarpine from *S. pachycarpa*, we have succeeded in isolating, by adsorption chromatography, two new crystalline bases (No. 1 and No. 2) which are described here. We have established, by circular paper chromatography, that the non-distilling fraction of the vat residues contains not less than six alkaloids. The distilling fraction (b. p. 205° at 5 mm) contains, according to our paper chromatography data, five alkaloids in addition to matrine and sophocarpine found previously [1].

Base No. 1 was isolated from the non-distilling fraction of the vat residues after preliminary extraction and dissolution in benzene; it can also be extracted from the propanol eluate obtained in the adsorption chromatography

\* For Communication VI see Zhur, Obshchei Khim. 30, 1744 (1960).

of the benzene solution of the non-distilling fraction. Its empirical formula is  $C_{15}H_{20}ON_2$ . It is optically inactive, gives a number of crystalline salts and the iodomethylate (Table 1), titrates as a monoacidic base, decolorizes acid potassium permanganate solution, and its salts are readily decomposed by ammonia. It remains unchanged when attempts are made to reduce it (zinc and hydrochloric acid, fuming hydriodic acid, electrolytic reduction, and catalytic reduction with platinum oxide). It contains neither the  $N-CH_3$  group nor active hydrogen.

The infrared spectrum of base No. 1 contains maxima characteristic of the  $N-CO$  group ( $1650\text{ cm}^{-1}$ ) and of the *trans*-quinolizidine group ( $2700-2800\text{ cm}^{-1}$ ) [8]. On the basis of the infrared and ultraviolet spectra (Figs. 1 and 2), and because the second nitrogen atom does not exhibit basic properties, it may be suggested that the base molecule contains the lactam ( $N-CO$ ) group, which is stable to acids and alkalis.

Base No. 1 is isomeric with anagryrine [9], termopsine [10, 11], leontidine [12, 13] and sophoramline [14], but differs from them in properties. Its infrared spectrum is somewhat reminiscent of tetracyclic compounds with two norlupinone rings.

Base No. 2, for which we propose the name *goebeline*,\* was isolated, like base No. 1, from the non-distilling fraction of the vat residues by the chromatography of its benzene solution on aluminum oxide. Goebeline was detected in both benzene and chloroform eluates. The residue after evaporation of the solvents was treated with ammonium iodide, and the hydriodide of goebeline was obtained.

The empirical formula of goebeline is  $C_{15}H_{22}ON_2$ ; its m. p. is  $231^\circ$ , and  $[\alpha]_D - 12.94^\circ$ . It forms crystalline salts and the iodomethylate (Table 1). Its salts are dextrorotatory: For example, the hydrobromide has  $[\alpha]_D + 21.01^\circ$ . Goebeline is stable to acids and alkalis, and titrates as a monoacidic base. Its solution in 10% sulfuric acid instantly decolorizes potassium permanganate solution. Its molecule contains neither the hydroxyl nor the  $N-CH_3$  group. On catalytic hydrogenation it absorbs 1 mole of hydrogen with the formation of the dihydro compound  $C_{15}H_{24}ON_2$  with m. p.  $207^\circ$  and  $[\alpha]_D + 42.28^\circ$ . The picrate of the hydrogenated product melts at  $192-193^\circ$  (decomp.) and the hydriodide at  $346-348^\circ$ .

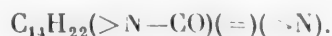
TABLE 2. Paper Chromatography of Alkaloids in the Vat Residues from *Sophora pachycarpa*

Vat residue fractions	$R_f$ Values of the alkaloids								
Distilling at $205^\circ$ (5 mm)	—	—	0.31	0.38	0.44	0.60	0.67	0.71	0.81
Non-distilling:									
a) Benzene eluate	—	0.24	0.33	0.38	0.44	—	—	0.70	—
b) Chloroform eluate	—	0.25	0.32	0.38	0.44	—	—	—	—
c) Propanol eluate	0.17	0.25	0.33	0.39	0.44	—	—	—	—

On reduction with lithium aluminum hydride, goebeline yields a monoacidic saturated desoxy base with the empirical formula  $C_{15}H_{26}N_2$ , m. p.  $198^\circ$  and  $[\alpha]_D + 14.21^\circ$ . Its picrate melts at  $216-217^\circ$  (decomp.), and the hydriodide at  $280-282^\circ$ .

The second nitrogen atom in the goebeline molecule does not exhibit acidic properties and apparently is present in the inert lactam group, which is frequently encountered in alkaloids of the  $C_{15}$  series. Its infrared spectrum (Fig. 3) also contains  $1658$ ,  $1678$  and  $2800\text{ cm}^{-1}$  bands. The first two show that the double bond in the goebeline molecule is not far from the lactam group, and the third points to the *trans*-disposition of the quinolizidine rings.

On the basis of these data the following expanded formula can be written for goebeline:



\* Goebelia Bge. is the name of the *Sophora* subspecies which includes *Sophora pachycarpa*.



Goebeline is isomeric with aphyllidine [15], rhombifoline [16], sophocarpine [3], monspessulanine [17] and base E isolated from *S. microphylla* Ait [18], but differs from them in properties.

Chemical studies on alkaloid No. 1 and goebeline are being continued.

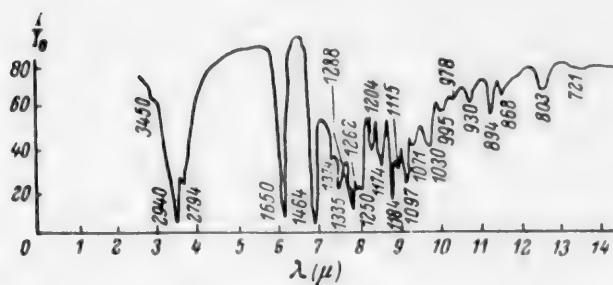


Fig. 1. Infrared spectrum of base No. 1.

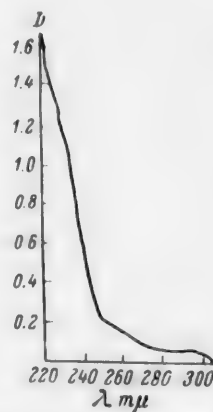


Fig. 2. Ultraviolet spectrum of base No. 1.

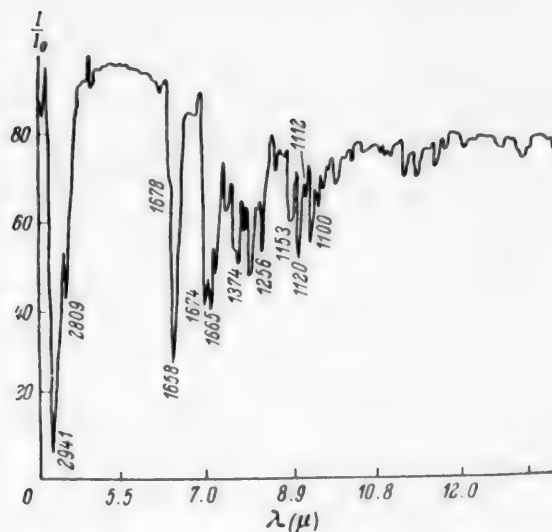


Fig. 3. Infrared spectrum of base No. 2 (goebeline).

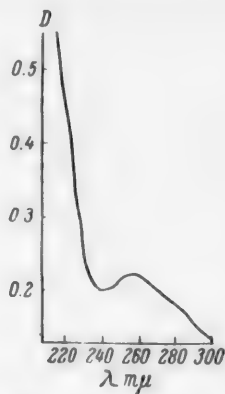


Fig. 4. Ultraviolet spectrum of base No. 2 (goebeline).

#### EXPERIMENTAL

**Base No. 1.** The vat residues (500 g) were distilled in a vacuum after preliminary extraction. Below 205° (at 5 mm), 250 g of the alkaloid mixture distilled off. The major part of the non-distilling residue (200 g) was dissolved

in dry benzene after repeated extraction. Crystals of base No. 1 separated from the solution on standing. The base begins to decompose markedly at 270° and does not melt below 300°. It is soluble in benzene, toluene and chloroform, is sparingly soluble in alcohol, and insoluble in ether, acetone and water.

Found %: C 73.31, 72.99; H 8.31, 8.21; N 11.40, 11.31. Equiv. wt. 246. Calculated for  $C_{15}H_{20}ON_2$ , %: C 73.77; H 8.19; N 11.43. Equiv. wt. 244.

**Base No. 2.** Part of the non-distilling residue (45 g) was dissolved in 300 ml of benzene and the solution passed through a column with aluminum oxide (900 g, column diameter 4 cm). The alkaloids were eluted from the column first with benzene, then with chloroform, and toward the end with propanol. The elution was continued until no more alkaloid could be detected in the solvent passing through. The solvent was distilled off from the propanol eluate, the residue was dissolved in benzene, and the solution chromatographed again on aluminum oxide (100 g, column diameter 2 cm). Crystals of base No. 1 separated from the benzene eluate.

When the residue obtained after distilling off the solvents from the benzene and chloroform eluates is treated with a saturated aqueous solution of ammonium iodide, crystalline goebeline hydriodide (5 g), which is sparingly

soluble in water, separates out. The hydriodide was dissolved in warm water, made alkaline with potash, and extracted with ether. After removal of part of the ether by distillation in the cold, crystals of goebeline separated from the solution. After recrystallization from ether, it melted at 231° and had  $[\alpha]_D^{20} - 12.94^\circ$  ( $c = 6.5$ , methanol). The base is readily soluble in methyl and ethyl alcohols, chloroform and benzene, sparingly soluble in acetone, ether and ligroin, and insoluble in petroleum ether and water.

Found %: C 73.56, 73.22; H 9.17, 9.21; N 10.77, 11.06. Equiv. wt. 246. Calculated for  $C_{15}H_{22}ON_2$ , %: C 73.17; H 8.94; N 11.38. Equiv. wt. 246.

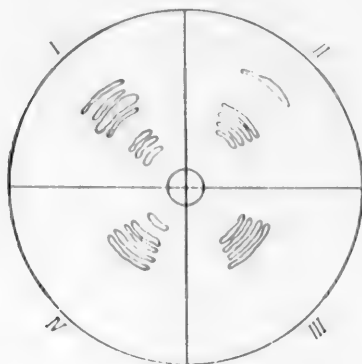


Fig. 5. Circular chromatogram of separate fractions of the *Sophora pachycarpa* vat residues. I) Distilling fraction; II) benzene eluate of the non-distilling fraction; III) chloroform eluate of the non-distilling fraction; IV) propanol eluate of the non-distilling fraction.

real extracts yielded 0.41 g of deoxygoebeline melting at 198° (recrystallized from 1:10 benzene-ether mixture), readily soluble in benzene, chloroform and alcohols, and sparingly soluble in ether.  $[\alpha]_D^{20} + 14.21^\circ$  ( $c = 0.74$ , ethanol).

Found %: N 11.90, 12.05. Equiv. wt. 230, 233. Calculated for  $C_{15}H_{26}N_2$ , %: N 11.96. Equiv. wt. 234.

The picrate of the deoxy product (recrystallized from alcohol) melts with decomposition at 216-217°; the hydriodide (recrystallized from an alcohol-acetone mixture) melts at 280-282°.

**Paper Chromatography of Alkaloids in the Vat Residues from *Sophora pachycarpa*.** Paper from the Volodarskii Leningrad No. 2 plant was used for the chromatography. The solvent was butanol-hydrochloric acid-water (50:7:13.5); the duration of the chromatography was 70 hr at 18°. The chromatographs were developed with Dragendorff's reagent (Fig. 5). The individual alkaloid spots were identified by means of "markers." The following  $R_f$  values were established: matrine 0.67, sophocarpine 0.71, pachycarpine 0.60, goebeline 0.38 and base No. 1, 0.17.

#### SUMMARY

1. From the non-distilling fraction of the vat residues from pachycarpine manufacture, two crystalline bases have been isolated and characterized.
2. A method for circular paper chromatography of alkaloids contained in the vat residues from the pachycarpine manufacture has been developed.

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# LETTERS TO THE EDITOR

## METHYL- AND VINYLACETYLENYLBORIC ESTERS

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Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 7,

pp. 2433-2434, July, 1961

Original article submitted March 22, 1961

Acetylene derivatives of boron have been studied very little. Only complexes of triphenylacetylenylboron [1, 2], diphenylalkynylboron [3] and bisdialkylboroacetylenes [4] are known. Boron compounds containing vinylacetylene groups have not been described.

The action of methylacetylenyl- and vinylacetylenylmagnesium bromides on tributyl borate at  $-40^{\circ}$  with subsequent treatment of the mixture with the calculated amount of 10% hydrochloric acid yielded the dibutyl esters of methyl- and vinylacetylenylboric acids.

### Dibutyl methylacetylenylborate.

B. p.  $103^{\circ}$  (10 mm),  $d_4^{20}$  0.8582,  $n_D^{20}$  1.4212.

Found %: C 67.26, 67.56; H 10.54, 10.75; B 4.89, 5.08.  $C_{11}H_{21}O_2B$ . Calculated %: C 67.37; H 10.79; B 5.52.

In the infrared spectrum of the substance, an intense band at  $2206\text{ cm}^{-1}$  corresponded to the triple bond and a band at  $1325\text{ cm}^{-1}$  to the B-O bond.

When hydrogenated over Pd/CaCO<sub>3</sub>, the substance added 1 mole of H<sub>2</sub>, and when brominated, 1 mole of bromine. The dibromide had a band of valence vibrations of the double bond at  $1640\text{ cm}^{-1}$  and of CH deformation vibrations at  $962\text{ cm}^{-1}$ . The spectrum also contained the apparently composite frequency of  $1737\text{ cm}^{-1}$ .

### Dibutyl vinylacetylenylborate.

B. p.  $109-110^{\circ}$  (10 mm),  $d_4^{20}$  0.8614,  $n_D^{20}$  1.4370.

Found %: C 69.04, 69.11; H 10.34, 10.31; B 5.29, 5.09.  $C_{12}H_{21}O_2B$ . Calculated %: C 69.25; H 10.17; B 5.20.

The infrared spectrum showed an intense band of the triple bond at  $2180\text{ cm}^{-1}$ , a double bond band of medium intensity at  $1597\text{ cm}^{-1}$  and a very intense band of the B-O bond at  $1340\text{ cm}^{-1}$ . The normal frequencies of 922 and  $965\text{ cm}^{-1}$  corresponded to the CH deformation vibrations of the vinyl group. The low intensity of the double bond band may be connected with association of this bond with the boron atom.

When hydrogenated over Pd/CaCO<sub>3</sub>, the substance absorbed 2 moles of H<sub>2</sub> to form the butenylboric ester, whose infrared spectrum contained a double bond band at  $1620\text{ cm}^{-1}$  and a band at  $966\text{ cm}^{-1}$  which apparently corresponded to CH deformation vibrations of the unsaturated group.

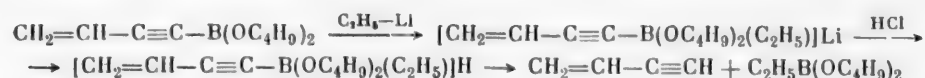
In bromination, the first bromine molecule added preferentially at the double bond. The infrared spectrum of the dibromide contained two triple bond frequencies of 2181 and  $2205\text{ cm}^{-1}$ .

In an attempt at the replacement of the butoxyl radicals by ethyl radicals by the action of ethyllithium at  $-70^{\circ}$ , we obtained the dibutyl ester of ethylboric acid.

B. p.  $77-78^{\circ}$  (10 mm),  $d_4^{20}$  0.8331,  $n_D^{20}$  1.4140.

Found %: C 65.34, 65.33; H 12.05, 12.30; B 5.20, 5.17.  $C_{10}H_{23}O_2B$ . Calculated %: C 64.53; H 12.46; B 5.81.

The reaction apparently proceeded by the mechanism proposed previously for aromatic compounds of boron[5].



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TRITERPENES OF THE BARK OF *Alnaster fruticosus* Ledeb.

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and I. A. Saltykova

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Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 7,

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Original article submitted March 6, 1961

From the bark of *Alnaster fruticosus* Ledeb., collected in the Krasnoyarsk region, we isolated the triterpenes: alnincanone [1], taraxerone and taraxerol acetate, which was found in plants for the first time. The solvent was removed from the chloroform extract of 8.4 kg of bark and the residue treated with ether. The ether-insoluble material was recrystallized from benzene and then from a mixture of chloroform and methanol (2 : 1). This yielded 1.45 g of pure taraxerone and 1.93 g of taraxerol acetate with m. p. 284-285°.

After extraction of the acids from it, the ether solution was evaporated and the residue dissolved in benzene and chromatographed on alumina (2nd activity). By washing the column with dry benzene, we obtained 3 fractions. From the 1st fraction we isolated taraxerol acetate (m. p. 285-288° from a mixture of ethanol and benzene); the 2nd fraction contained 8.2 g of crude alnincanone (m. p. 156-162°); from the 3rd fraction we isolated 12.5 g of a mixture (m. p. 160-204°) which could not be separated into components.

Identification of alnincanone. After further purification, the substance had m. p. 169-171.5°. A mixed melting point with alnincanone isolated from *Alnus incana* [1] (m. p. 171-171.5°) was not depressed.

Found %: C 81.07; H 11.63.  $C_{30}H_{52}O_2$ . Calculated %: C 81.02; H 11.79.

The 2, 4-dinitrophenylhydrazone of the substance investigated had m. p. 234-235° and did not depress the melting point of the 2, 4-dinitrophenylhydrazone of alnincanone (m. p. 235° [1]).

The infrared spectra of the substance with m. p. 169-171.5° and authentic alnincanone in the region of 1200-800  $cm^{-1}$  were identical.

Identification of taraxerol acetate. After repeated recrystallization, the taraxerol acetate melted at 299-300°.

Found %: C 81.85; H 11.36.  $C_{32}H_{52}O_2$ . Calculated %: C 81.99; H 11.18.

The infrared spectrum of this substance contained a strong band in the region where ester carbonyl groups absorb.

A 0.42 g sample of this substance was dissolved in 15 ml of benzene and hydrolyzed by heating for 2 hr with 30 ml of a 10% alcohol solution of potassium hydroxide. The usual treatment yielded 0.38 g of a hydrolysis product with m. p. 278-280°. A mixed melting point with taraxerol [m. p. 282° (corr.)] was not depressed.

Found %: C 84.64; H 11.91.  $C_{30}H_{50}O$ . Calculated %: C 84.67; H 12.03.

Authentic taraxerol (0.1 g) was acetylated in the usual way with acetic anhydride in pyridine. The melting point of the acetate obtained was 298-300°. A mixed melting point with the substance isolated from the bark of *Alnaster fruticosus* was not depressed.

Identification of taraxerone. After two recrystallizations, the substance had a constant melting point of 241-245°. A mixed melting point with taraxerone [1] (m. p. 238-240°) was not depressed.

Found %: C 84.75; H 11.63.  $C_{30}H_{48}O$ . Calculated %: C 84.84; H 11.39.

The infrared spectrum of the substance investigated contained an intense absorption band in the region of carbonyl frequencies.

The oxime of the ketone investigated melted at 283-285° and did not depress the melting point of the oxime of authentic taraxerone (m. p. 285-287°).

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# REACTION OF SODIOACETOACETIC ESTER WITH $\alpha$ -BROMO OXIDES

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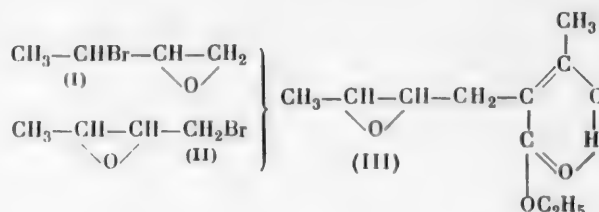
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 7,

pp. 2435-2436, July, 1961

Original article submitted March 2, 1961

As a development of the study of the reaction of nucleophilic reagents with  $\alpha$ -bromo ketones (compounds which have two electrophilic centers in adjacent positions), it seemed interesting to extend the investigation to  $\alpha$ -bromo oxides.

We studied the reaction between Na-acetoacetic ester and two isomeric  $\alpha$ -bromo oxides: 3-bromo-1, 2-epoxybutane (I) and 1-bromo-2, 3-epoxybutane (II). The same substance was obtained in both cases and this was the product of C-alkylation of acetoacetic ester (III). In both cases the reaction occurred at the terminal carbon atom; in the first case there was opening of the oxide ring with subsequent displacement of the bromine and the formation of an oxide ring in the neighboring position; in the second case there was direct replacement of the bromine by the acetoacetic ester residue.

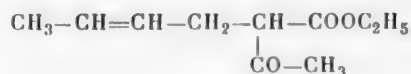


The substance obtained, the enol form of 2, 3-epoxybutylacetoacetic ester (III), was analyzed and had the following constants:

B.p. 113-114° (1 mm),  $d_4^{20}$  1.1092,  $n_D^{20}$  1.4897,  $\overline{MR}_D$  52.17; calc. 51.49.

Found %: C 60.15, 59.89; H 8.20, 8.10;  $H_{act}$ , 0.8.  $C_{10}H_{16}O_4$ . Calculated %: C 59.98; H 8.05;  $H_{act}$ , 1.

The same product was obtained by confirmatory synthesis by oxidation of  $\alpha$ -crotylacetoacetic ester with benzoyl hydroperoxide.



B. p. 114-115° (1 mm),  $n_D^{20}$  1.4928,  $d_4^{20}$  1.1205,  $\overline{MR}_D$  51.92. Found %: C 60.32, 60.31; H 7.75, 7.84.

The infrared spectra of all three compounds were identical. Intense absorption bands were observed in the regions of 1699  $\text{cm}^{-1}$  (ester carbonyl conjugated with a double bond and bound by an intramolecular hydrogen bond), 1657  $\text{cm}^{-1}$  ( $-\text{C}=\text{C}$  bond), 897  $\text{cm}^{-1}$  ( $\alpha$ -oxide ring, trans-form) and 834  $\text{cm}^{-1}$  ( $\alpha$ -oxide ring, cis-form), while the frequencies of 917 and 840  $\text{cm}^{-1}$ , characteristic of an  $\alpha$ -oxide ring at the end of a chain, were completely absent.

Hydrolysis of (III) with NaOH yielded methyl- $\gamma$ ,  $\delta$ -dihydroxyamyl ketone.

B. p. 102° (1 mm),  $n_D^{20}$  1.4651.

Found %: C 57.56, 57.45; H 9.68, 9.66.  $H_{act}$ , 1.92, 2.20.  $C_7H_{14}O_3$ . Calculated %: C 57.51; H 9.65;  $H_{act}$ , 2.



The same compound was obtained by confirmatory synthesis by oxidation of crotylacetone with barium permanganate.

B. p. 102° (1 mm) and  $n_D^{20}$  1.4630.

Found %: C 57.72, 57.97; H 8.93, 9.10.

The infrared spectra of the two substances were identical ( $\lambda_{\max}$  1700  $\text{cm}^{-1}$ ).

Oxidation of the product (III) with periodic acid gave acetaldehyde (2, 4-dinitrophenylhydrazone, m. p. 147°) and the involatile oil gave a derivative with p-nitrophenylhydrazine with m. p. 288° (subl.).

## LIQUID - PHASE HYDRATION OF ACETYLENE WITH A COPPER CATALYST

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We previously proposed a new method for the liquid-phase hydration of acetylene to acetaldehyde by means of a copper catalyst [1, 2]. The latter consists of an aqueous solution of cuprous chloride, ammonium chloride, sulfuric acid, and a small amount (0.1-0.5%) of sulfides of various metals or hydrogen sulfide [1]. Our subsequent investigations in this field showed that the hydration of acetylene by the above method [1, 2] proceeds smoothly when sulfuric acid is replaced by other mineral acids (2-5% of HCl,  $\text{HClO}_4$ , or  $\text{H}_3\text{PO}_4$ ) or organic acids (5-15% of oxalic or mono- or trichloroacetic acid) as the acid component. In this case the best results were obtained with hydrochloric acid; with the other acids given above, the reaction was sometimes accompanied by precipitation of the catalyst.

It was shown that instead of adding sulfides of various metals or hydrogen sulfide to the catalytic solution, as was done previously [1, 2], it was possible to use various organic compounds containing a sulfhydryl group (octyl mercaptan, mercaptosalicylic acid, thioglycol, p-alkoxythiobenzoic acid, etc.). For the work we used 0.5 liter of catalytic solution; the acetylene input rate was varied from 15-50 liters/hr and the temperature was 80-85°. The working and product analysis procedures were as previously described [1].

Depending on the input rate, the acetylene conversion reached 30% and the acetaldehyde yield, 90%. With an increase in the rate at which acetylene was passed through the catalytic solution, there was an increase in the amount of acetaldehyde in g/hr, but there was a decrease in the degree of conversion of acetylene.

### LITERATURE CITED

1. S. A. Vartanyan, S. K. Pirenyan and N. G. Manasyan, *Izv. AN Arm. SSR, SKhN* **12**, 345 (1959).
2. S. A. Vartanyan and S. K. Pirenyan, Author's Certificate 623030 from March 23, 1959.

# REACTION OF ETHYLENIMINE WITH THE TRIMER OF PHOSPHONITRILE CHLORIDE

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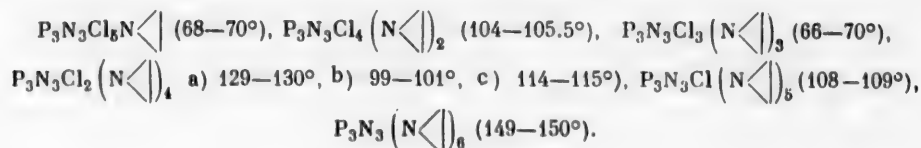
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 7,

p. 2437, July, 1961

Original article submitted March 22, 1961

We studied the reaction of ethylenimine with the trimer of phosphonitrile chloride, which had not been investigated previously. It was established that by varying the reaction conditions it was possible to replace the chlorine atoms, beginning with one and ending with six; the chlorine atoms could be replaced with the formation of compounds with both odd and even numbers of ethylenimino groups; isomerism was also observed.

The compounds obtained were as follows (melting points in brackets):



# REACTION OF NITROSYL CHLORIDE WITH DIALLYL AND BUTADIENE

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pp. 2438-2439, July, 1961

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We investigated the reaction of nitrosyl chloride with diallyl and butadiene under the conditions of the reaction with olefins, i.e., in ether without hydrogen chloride and in the presence of hydrogen chloride, with various molar ratios of the reagents.

The products from the reaction without hydrogen chloride with a molar ratio of nitrosyl chloride : diallyl of 1,9:1 were found to contain 5, 6-dichlorohexene-1 (b. p. 60,5-61,5° at 10 mm,  $d_4^{20}$  1.0674,  $n_D^{20}$  1.4641) and 6-nitro-5-chlorohexene-1 (b. p. 78-79° at 3 mm,  $d_4^{20}$  1.1407,  $n_D^{20}$  1.4695), while at a reagent ratio of 3:1, in addition to the above unsaturated compounds, we isolated a mixture of 1, 6-dinitro-2, 5-dichlorohexane and 1,2,5, 6-tetrachlorohexane, which could not be separated by distillation because of decomposition.

The given composition of the mixture was confirmed by elementary analysis for nitrogen and chlorine, the infrared spectra, and hydrolysis to meso- $\alpha, \alpha'$ -dichloroadipic acid. Dichlorodinitrohexane predominated in the mixture forming the high-boiling fraction, as was shown by the high refractive index ( $n_D^{20}$  1.525), the percentage chlorine content (36,02%), and the considerable yield of meso- $\alpha, \alpha'$ -dichloroadipic acid when the crude product was heated with concentrated hydrochloric acid in sealed ampoules (2 g of acid with m. p. 187-188° from 5,5 g of the mixture).

Thus, diallyl behaves like monosubstituted olefins in the reaction with nitrosyl chloride [1].

In the presence of hydrogen chloride, diallyl reacted with nitrosyl chloride to form the diacid chloride of dichloroadipohydroxamic acid ( $\text{HON}=\text{CCl}-\text{CHCl}-\text{CH}_2-\text{CH}_2$ ).

The substance isolated formed crystals with m. p. 128-129° (from benzene). The composition and structure of the reaction product were confirmed by complete elementary analysis, determination of the active hydrogen, the infrared spectra, and hydrolysis to meso- $\alpha, \alpha'$ -dichloroadipic acid (m. p. 184-185°). Thus, in the presence of hydrogen chloride, diallyl reacts in the same way as monosubstituted olefins [2].

The reaction of nitrosyl chloride with butadiene in the absence of hydrogen chloride with equimolar ratios of the reagents gave a mixture of 3,4-dichlorobutene-1, 4-nitro-3-chlorobutene-1 and 1,4-dinitro-2,3-dichlorobutane (analysis, infrared spectra and hydrolysis to meso- $\alpha, \alpha'$ -dichlorosuccinic acid), while with a molar ratio of nitrosyl chloride:butadiene of 3,9:1, from the reaction products we isolated crystalline 1,4-dinitro-2,3-dichlorobutane (m.p. 163-164°) and liquid products whose structure was not determined.

The formation of these compounds indicates that butadiene behaves like a diolefin, i.e., the double bonds react independently. The structure of 1, 4-dinitro-2, 3-dichlorobutane was demonstrated by its conversion by heating with concentrated hydrochloric acid into meso- $\alpha, \alpha'$ -dichlorosuccinic acid (m.p. 215-216°).

The products from the reaction of butadiene with nitrosyl chloride in the presence of hydrogen chloride were found to contain 3, 4-dichlorobutene-1 (b. p. 122-124° at 773 mm,  $d_4^{20}$  1.1491,  $n_D^{20}$  1.4648), the oxime of an unsaturated chloro aldehyde [the oxime of 2-chlorobuten-3-al or 4-chlorobuten-2-al, m. p. 142-143° (decomp.)] and the dioxime of  $\alpha, \alpha'$ -dichlorosuccinaldehyde [m. p. 157,5-158° (decomp.)], as was confirmed by analysis and the infrared spectra.

The formation of acid chlorides of the corresponding hydroxamic acids during the reaction was demonstrated qualitatively (hydrolysis of the crude product and reaction with  $\text{FeCl}_3$ ).

#### LITERATURE CITED

1. K. A. Ogloblin, ZhOKh 28, 3245 (1958) ; 27, 2541 (1957).
2. K. A. Ogloblin, ZhOKh 29, 264 (1959).

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

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# Soviet Journals Available in Cover-to-Cover Translation

ABBREVIATION	RUSSIAN TITLE	TITLE OF TRANSLATION	PUBLISHER	TRANSLATION BEGAN
				Vol. Issue Year
AÉ	Atomnaya énergiya	Soviet Journal of Atomic Energy	Consultants Bureau	1 1 1956
Akust. zh.	Akusticheskiy zhurnal	Soviet Physics — Acoustics	American Institute of Physics	1 1 1955
Astr.(on). zh(urn).	Antibiotiki	Antibiotics	Consultants Bureau	4 1 1959
Avto(mat). svarka	Astronomicheskii zhurnal	Soviet Astronomy—AJ	American Institute of Physics	34 1 1957
	Astronomicheskaya svarka	Automatic Welding	British Welding Research Association (London)	
	Avtomatika i Telemekhanika	Automation and Remote Control	Instrument Society of America	1 1959
	Biotizika	Biophysics	National Institutes of Health*	27 1 1956
	Biokhimiya	Biochemistry	Consultants Bureau	21 1 1957
Byull. éksp(erim). biol. i med.	Byulleten' éksperimental'noi biologii i meditsiny	Bulletin of Experimental Biology and Medicine	Consultants Bureau	41 1 1959
DAN (SSSR)	Doklady Akademii Nauk SSSR	The translation of this journal is published in sections, as follows:		
Dokl(ady) AN SSSR		Doklady Biochemistry Section	American Institute of Biological Sciences	106 1 1956
		Doklady Biological Sciences Sections (Includes: Anatomy, biophysics, cytology, ecology, embryology, endocrinology, evolutionary morphology, genetics, histology, hydrobiology, microbiology, morphology, parasitology, physiology, zoology sections)	American Institute of Biological Sciences	112 1 1957
		Doklady Botanical Sciences Sections (Includes: Botany, phytopathology, plant anatomy, plant ecology, plant embryology, plant physiology, plant morphology sections)		
		Proceedings of the Academy of Sciences of the USSR, Section: Chemical Technology	Consultants Bureau	106 1 1956
		Proceedings of the Academy of Sciences of the USSR, Section: Chemistry	Consultants Bureau	106 1 1956
		Proceedings of the Academy of Sciences of the USSR, Section: Physical Chemistry	Consultants Bureau	112 1 1957
		Doklady Earth Sciences Sections (Includes: Geochemistry, geology, geophysics, hydrogeology, mineralogy, paleontology, petrography, permafrost sections)	American Geological Institute	124 1 1959
		Proceedings of the Academy of Sciences of the USSR, Section: Geochemistry	Consultants Bureau	106-1 1957-1958
		Proceedings of the Academy of Sciences of the USSR, Section: Geology	Consultants Bureau	106-1 1957-1958
		Doklady Soviet Mathematics	The American Mathematics Society	123 6 1958
		Soviet Physics—Doklady (Includes: Aerodynamics, astronomy, crystallography, cybernetics and control theory, electrical engineering, energetics, fluid mechanics, heat engineering, hydraulics, mathematical physics, mechanics, physics, technical physics, theory of elasticity sections)		131 1 1961
		Proceedings of the Academy of Sciences of the USSR, Applied Physics Sections (does not include mathematical physics or physics sections)	American Institute of Physics	106 1 1956
		Wood Processing Industry		
		Telecommunications	Consultants Bureau	106-1 1956-1957
		Entomological Review	Timber Development Association (London)	9 1959
		Pharmacology and Toxicology	Massachusetts Institute of Technology*	1 1957
		Physics of Metals and Metallurgy	American Institute of Biological Sciences	38 1 1959
		Sechenov Physiological Journal USSR	Consultants Bureau	20 1 1957
		Plant Physiology	Acta Metallurgica*	5 1 1957
		Geochemistry	National Institutes of Health*	1 1957
		Soviet Physics—Solid State	American Institute of Biological Sciences	4 1 1957
		Measurement Techniques	The Geochemical Society	1 1958
		Bulletin of the Academy of Sciences of the USSR: Division of Chemical Sciences	American Institute of Physics	1 1959
			Instrument Society of America	1 1959
			Consultants Bureau	1 1952
Derevoobrabat. prom-st.	Derevoobrabatnyy vuyushchaya promyshlennost'			
Éntom(ol). oboz(renie)	Élektrosvyaz			
Farmakol. (i) toksikologiya)	Entomologicheskoe obozrenie			
FMM	Fizika metallov i toksikologiya			
Fiziol. zhurn. SSSR	Fizika metallov i metallovedenie			
(im. Sechenova)	Fiziologicheskii zhurnal im. I. M. Sechenova			
Fiziologiya) rastenii	Fiziologiya rastenii			
FTT	Geokhimiya			
Izmerit. tekhnika)	Fizika tverdogo tela			
Izv. AN SSSR,	Izmeritel'naya tekhnika			
O(td). Kh(im). N(suk)	Izvestiya Akademii Nauk SSSR: Otdelenie khimicheskikh nauk			

Izv. AN SSSR,  
O(td). T(ekhn). N(auk):  
Met(all). i top.  
Izv. AN SSSR Ser. fiz(ich).

\*Sponsoring organization. Translation through 1960 issues is a publication of Pergamon Press.



